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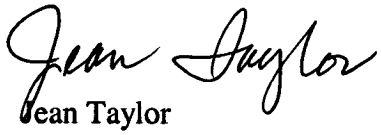

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Abstract

The major objective of this study was to determine whether high birth weight is associated with ALL and AML among children and to quantify the strength of the relationships. We conducted a meta-analysis of nine case-control studies (published between 1991 and 2004) encompassing over 6,200 children with ALL and over 12,000 controls. We found that children weighing 4,000 g or more at birth had 24% (OR: 1.24; 95% CI: 1.12, 1.37) higher odds of developing ALL than children weighing less (without consideration to reference weight). Regardless of peer-review status, response rates among cases and controls, or choice of threshold for high birth weight, studies consistently demonstrated a similar overall odds ratio ranging from 1.23 to 1.29. In addition, our data analysis identified possible reasons for inconsistent findings among previous studies that examined high birth weight as a risk factor for ALL. Possible explanations include: use of different reference birth weights, different data source for birth weight (i.e., birth certificate vs. interview), and different ethnic makeup of the study population. Our data supports the growing evidence for the link between high birth weight and childhood ALL. Women who are pregnant or considering pregnancy should know that unbounded weight gain may increase the odds of childhood ALL in their baby. Whether a positive association with high birth weight applies to AML is less clear from our results. Based on a meta-analysis of only three case-control studies (published between 1997 and 2004) involving over 700 children with AML and over 1,900 controls, high birth weight ($\geq$ 4,000 g) appeared to increase the odds of developing AML by 14% (OR: 1.14; 95% CI: 0.84, 1.54).

Birth Weight and Acute Childhood Leukemia: A Meta-analysis of Observational Studies

Doctoral Dissertation
March 22, 2005

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DEDICATION

I dedicate this doctorate thesis to my parents and to my son. My father, the late Dr. Shu-Ren Lin, was an accomplished neuroradiologist who instilled in me the values of hard work, persistence, and excellence. My mother, Mrs. Yie-Chen Lin, exemplifies generosity, self-sacrifice, and unwavering love. She helped care for my son and provided support that was immeasurable. Her name deserves to be along side mine on my diploma. Lastly, I want to thank my eleven-year-old son, Trevor Taylor, who when told that I was near completion asked, “Mom, does this mean that you’ll be making more money?” I replied, “Believe it or not, I did not go back to school for a job promotion but simply for the sheer joy of learning.” To this he shook his head and responded, “Mom, you and I are way different.”

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1. BACKGROUND AND INTRODUCTION

1.1 Childhood Acute Leukemia

The leukemias of childhood are cancers of the hematopoietic system, affecting cells involved in blood formation and development.[1] Leukemia occurs when immature white blood cells multiply in an uncontrolled manner in the bone marrow.[1] It is classified as lymphoid or myeloid, according to the type of cell that is multiplying abnormally, and acute or chronic, depending on the speed of progression of disease.[1] Acute lymphoblastic leukemia (ALL) begins in immature B and T lymphocytes while acute myeloid leukemia (AML) begins in immature myeloid (i.e., non-lymphoid) cells.[1]

1.1.1 Occurrence

Leukemias account for the largest number of cases of cancer in children, representing one-third of all malignancies in children younger than 15 years of age in the United States.[2] In addition, leukemias are the primary cause of cancer related mortality in children in the United States.[2] The age-adjusted incidence of ALL and AML is 26.3 per million and 6.5 per million, respectively.[141] Approximately 2,700 children in this age group are diagnosed with leukemia each year in the United States, of which about 80% are ALL, 15% are AML, and 5% belong to the chronic leukemia category.[2]

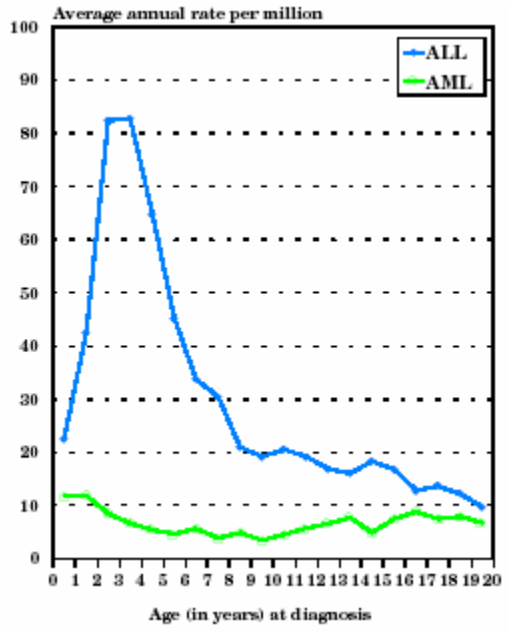
Incidence of ALL in children varies by age, sex, and race. A sharp peak of

disease incidence occurs at ages 2-3 years (Figure 1).[2] Males have a higher incidence of ALL (about 20%) than females, while white children have an approximate two-fold higher risk than black children.[2] Incidence of AML in children also varies with age (Figure 1), but with a different pattern than that for ALL. AML rates are highest in the first 2 years of life, but subsequently decrease until 10 years, followed by generally increasing rates thereafter.[2] Unlike ALL, the incidence of AML does not vary by sex and is similar in black children and white children. [2]

1.1.2 Trends

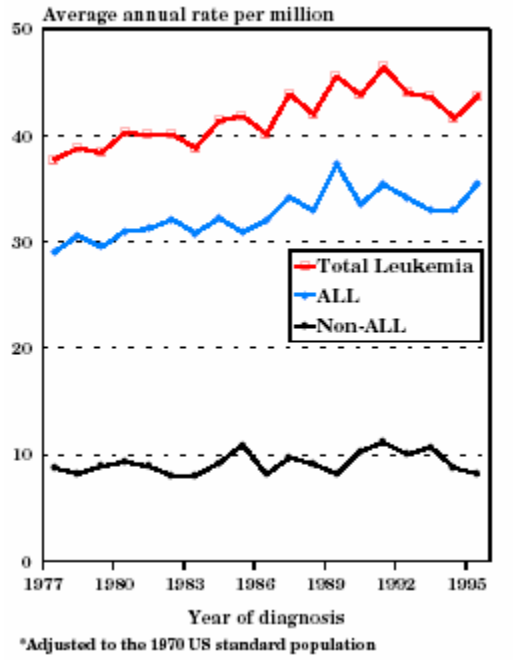
The incidence of leukemia among children moderately increased in the past 20 years (Figure 2), with the trend primarily reflecting an increase in ALL incidence during this period.[2] While the overall incidence rate has increased since the mid-1970's, death rates have declined dramatically. Overall survival for children with ALL is now approximately 80%, attributable primarily to improvements in treatment.[2] Outcome for children with AML also has improved, but 5-year survival rates have increased to only about 40%.[2]

Figure 1. ALL (1986-94) and AML (1976-84 and (1986-94) age-specific incidence rates, SEER**



**SEER=Surveillance, Epidemiology and End Results

Figure 2. Trends in leukemia and ALL age-adjusted* incidence rates, age <15 years, SEER**, 1977-95



1.1.3 Risk Factors

While ALL is the predominant form of cancer in children, its causes and risk factors remain largely unknown. A few factors, such as Down's Syndrome, other specific genetic abnormalities, being an identical twin of a sibling with leukemia, and ionizing radiation exposure (both *in utero* and postnatal), have been conclusively linked to ALL but explain only a small fraction of cases.[3] A plausible etiologic explanation is lacking for more than 90% of cases of childhood leukemia.[4] Table 1 summarizes the known risk factors for childhood ALL with reported magnitudes of risk.

Some different risk factors distinguish childhood AML from ALL. For example, exposure to specific chemotherapeutic agents has been associated

with an increased risk of childhood AML, in contrast to ALL. Table 2 summarizes the established risk factors for childhood AML.

Table 1. Known risk factors of acute lymphoblastic leukemia (ALL) in children

Exposure or Characteristic	Comments	References
Sex	Males have a 20% higher incidence than females.	3, 5, 6
Age	There is a peak in the incidence at ages 2-3 years.	3, 5, 6
Race	White children have a 2-fold higher risk than black children.	3, 5, 6
Ionizing radiation (*in utero*)	Prenatal diagnostic x-ray exposure has been associated with an increased risk (about 1.5 fold).	3, 5, 6, 7
Ionizing radiation postnatal (therapeutic)	Therapeutic radiation for such conditions as tinea capitis and thymus enlargement has been associated with an increased risk (about 2.0 fold).	3, 5, 6, 8, 9
Being an identical twin of a child with leukemia	Risk in the unaffected twin is as high as 25% early in life.	4, 8
Down syndrome, neurofibromatosis, Shwachman syndrome, Bloom syndrome, ataxia telangiectasia, Langerhans cell histiocytosis, and Klinefelter syndrome	Increased occurrence is associated with these genetic conditions and is particularly apparent in children with Down syndrome for whom there is about a 20-fold increased risk of leukemia.	3, 5, 6, 10

Table 2. Known risk factors of acute myeloid leukemia (AML) in children

Exposure or Characteristic	Comments	References
Chemotherapeutic agents	Increased risk is associated with prior exposure to alkylating agents or epipodophyllotoxins. Risk depends on the drug regimens and length of treatment and ranges between 1 and 20% (generally about 5%).	11, 12, 13
Ionizing radiation (*in utero*)	Prenatal diagnostic x-ray exposure has been associated with an increased risk (about 1.5 fold).	3, 5, 6
Down syndrome, neurofibromatosis, Shwachman syndrome, Bloom syndrome, familial monosomy 7, Kostmann granulocytopenia, Fanconi anemia	Increased occurrence associated with these genetic conditions, particularly with Down syndrome for whom there is about a 20-fold increased risk of leukemia.	3, 5, 6, 10

Some of the other reported, but less well-established risk factors for acute leukemia in children include prior fetal loss, maternal alcohol consumption during pregnancy, and advanced maternal age (≥ 35 years), among others. Some studies showed an increased risk (as high as 1.6 fold [95% CI=1.0-2.7]) of childhood leukemia (both ALL and AML) with maternal history of fetal loss[14-16] while one study reported an inverse association.[17] Some studies showed an increased risk of AML with maternal alcohol consumption during pregnancy (as high as 3.0 fold [95% CI=1.2-8.4])[15,18,19] while other studies failed to demonstrate such an association.[15,16] Similarly, the association with advanced maternal age (≥ 35 years) has been inconsistent; some studies found an increased risk of ALL (as high as two-fold [95% CI=1.3-3.6]),[14] whereas others reported no increased risk.[20]

The association between high birth weight and risk of childhood acute leukemia, primarily ALL, has been the subject of many investigations.[14,15,20-32] A number of studies report an elevated risk of childhood ALL among those with a high birth weight (generally over 4000 grams or 8 pounds, 14 ounces).[14, 20-22, 23-27] The odds ratio of ALL reported in these studies ranges from 1.4 (95% CI=1.1-1.8)[22] to 2.5 (95% CI=1.2-5.4).[23] This finding appears to be strongest for children diagnosed with ALL at younger ages.[14,25,29,32] While many studies document an association between high birth weight and the risk of ALL, other studies fail to demonstrate this association.[33-34] Although the majority of studies defined high birth weight as over 4,000 grams, a few use a different cut-off weight including over 3500 grams[21,35] and over 4500 grams.[24]

For AML, there appears to be far fewer studies reporting an association with high birth weight; most studies failed to show a relationship.[15,23,26,33] However, one study confirmed an association between AML and high birth weight, reporting an odds ratio of 6.2 (95% CI=1.3-29.8).[35] Another study reported an odds ratio of 2.5 (95% CI=1.1-5.5) among children diagnosed before 2 years of age but failed to demonstrate such a relationship among children diagnosed after 2 years.[27]

The reported link between high birth weight and risk of childhood acute leukemia has received not only national but also international interest. In March 2002, the National Institutes of Health (NIH) convened an international workshop devoted to gene-environment interactions in childhood cancer research.[36] At this workshop, Dr. Michele R. Forman (Principle Investigator, Center for Cancer Research, National Cancer Institute) reviewed the scientific evidence supporting the approximately two-fold increased risk of childhood and infant ALL and AML in high birth weight babies compared to children with normal birth weights.[36] Following the symposium, Dr. Forman and other researchers spearheaded a pooled analysis of individual level data from different studies to examine the relationship of birth weight to ALL and AML. An international collaboration comprising over eight major research centers are involved in this pooled analysis. In a pooled analysis, the original patient-level data are obtained from investigators and analyzed using common definitions, coding, and endpoints for variables.[37] This present study is not a pooled analysis. Rather it is a meta-analysis, the idea of which originated with Dr. Forman.

1.1.4 Clinical presentation

Common symptoms of ALL include fever, abdominal distension, bruising, mucous membrane bleeding, and bone or joint pain.[148] Common physical examination findings include lymphadenopathy, splenomegaly, hepatomegaly, petechiae, and purpura.[148] Evaluation typically includes a complete blood count, chemistry panel, chest x-ray, lumbar puncture, and bone marrow aspiration. [148] Over half of children diagnosed with ALL, initial white blood count is within normal limits; however, a carefully performed differential examination of leukocytes usually reveals neutropenia and lymphoblasts.[148] Thrombocytopenia (platelet count < 100,000/mm^3) is evident in about 75% of children diagnosed and anemia (hemoglobin < 10 g/dl) is present in 80% of cases.[148]

1.1.5 Diagnostic classification

The diagnosis of ALL is confirmed with bone marrow aspiration is positive for at least 25% lymphoblasts. Childhood ALL is classified as B-cell precursor (83% of cases), mature B-cell (2% of cases), or T-cell (15% of cases), reflecting the stage at which lymphoid cell differentiation is blocked in the malignant clone.[4] Morphologic evaluation classifies leukemic cells based on physical features that are visible under the microscope (e.g., size, shape, amount of cytoplasm).[4] In 1976, the French-American-British (FAB) Cooperative Working Group identified three morphologic subtypes of ALL (L1, L2, and L3). The FAB classification system has become internationally accepted as the standard for morphologic assessment of lymphoblasts.[4]

1.2 Meta-analysis

1.2.1 Definition

A meta-analysis is a systematic approach to identify, assess, synthesize, and (if appropriate) combine the results of similar but independent studies.[37] Studies are the primary unit of analysis, in contrast to a pooled analysis. In a meta-analysis, individual study results are combined to give a summary estimate of effect weighted by the inverse of the variance, so that studies with smaller variances receive more weight.[37]

The overall steps of a meta-analysis include the following:[38]

1. Identify all relevant studies
2. Apply pre-defined inclusion and exclusion criteria
3. Abstract data from each eligible study
4. Analyze the data statistically
    a. Evaluate heterogeneity across all studies
    b. Combine data to get a summary estimate of effect and its confidence interval, (if appropriate)
    c. Assess for potential publication bias
    d. Assess study quality
    e. Conduct sensitivity and subgroup analyses

1.2.2 Advantages

The main advantages of a meta-analysis include (1) speed and economy, (2) enhanced statistical power, (3) enhanced precision, and (4) exploration of heterogeneity between study results and possible resolution when it is present.[37]

A meta-analysis requires less time and less expense to conduct than most primary research of equal size. By combining information over different studies, an integrated analysis will have more statistical power to detect an effect than an analysis based on only one study. Small studies may lack sufficient statistical power to demonstrate an effect. Combining the results of several studies through the techniques of meta-analysis can provide stronger evidence *for* or *against* an effect than that derived from any individual study. Stronger evidence is provided by a meta-analysis because it produces a more precise estimate of the effect (i.e., an estimate with a smaller standard error or a narrower confidence interval). Moreover, a meta-analysis can help clarify why studies show disparate results. For example, the possibility of different exposure or outcome definitions as an explanation for the discrepancy in estimates of effect can be examined.

Lastly, a quantitative systematic review, where a complete literature search is carried out, studies selected and data extracted in a reproducible and explicit fashion, is in keeping with evidence-based medicine (EBM). EBM is the process of systematically reviewing, appraising and using clinical research findings to aid in the delivery of optimum clinical care to patients.[39] A properly conducted meta-analysis provides an objective summary of large amounts of data. Given the enormity of research information available, health care providers may find it impossible to keep abreast of current developments or to translate them into clinical practice. For health care providers interested in the bottom line of evidence, meta-analyses can help focus the results of research and facilitate medicine that is evidence-driven.

1.2.3 Limitations

While the benefits of a meta-analysis are many, nevertheless there are limitations to this approach. First, results of a meta-analysis are no more reliable than the quality of the underlying studies upon which they are based. While combining data decreases the variation caused by random error (by increasing the sample size), it does not eliminate or reduce any systematic error (i.e., bias).[37] In other words, meta-analysis cannot compensate for bias in the original studies. For example, if the original studies fail to randomize properly, have an improper control group, misclassify exposure or disease, do not control adequately for confounding, have a low response rate or a high rate of loss to follow-up, meta-analysis will not remedy the problem.

Second, there is little or no control over data from individual studies. Selection of which data to collect and how the data are recorded are all predetermined; as such, important confounders (e.g., age, sex) may not have been measured or recorded.

Third, the validity of meta-analysis is critically dependent on the identification and consideration of all relevant studies. When a meta-analysis includes only published studies, publication bias is a potential problem. Publication bias refers to the greater likelihood of research with statistically significant results to be submitted and published than studies with non-significant (e.g., $p>0.05$) or null results (e.g., relative risk=1.0).[37] Bias in favor of publication of statistically significant results is well documented.[40-41] Publication bias has been attributed to (1) editorial policies that place higher value on studies that

report statistically significant associations, (2) a presumed partiality of journal reviewers against null and non-significant results, and (3) failure of investigators to submit for publication studies showing no effect.[37,42] Even with these limitations, a meta-analysis remains a useful and important tool for systematically synthesizing a body of research for the reasons listed earlier.

1.3 Specific aims and hypotheses

Since the association between high birth weight and childhood leukemia is uncertain, this present meta-analysis aimed to:

1. Clarify the relationship between high birth weight and ALL, and between high birth weight and AML among children under 18 years of age;
2. Determine whether the magnitude of effect varies by age at ALL or AML diagnosis; and
3. Explain the reasons for inconsistent findings among the studies evaluated.

Our a priori hypothesis was that the risk of ALL and of AML is higher among children who are born with birth weight greater than 4000 grams. Moreover, we hypothesized that the magnitude of effect does vary by age, with the strongest association appearing at younger ages (e.g., < 2 years).

1.4 Significance

Acute leukemia is the most predominant form of cancer in children, with poorly understood causes and risk factors. Observational studies that have examined one of these factors – high birth weight – show inconsistent results. A

meta-analysis has not been previously conducted.* Employing a meta-analysis to study the relationship between high birth weight and acute leukemia will (1) elucidate the mixed evidence in the literature, (2) advance scientific understanding, (3) guide clinical practice and policy, (4) suggest direction for future research and (5) provide a comparison for a pooled analysis on the same topic currently underway.

First, a meta-analysis will resolve uncertainty in the scientific literature concerning the relationship between high birth weight and acute leukemia by providing a more precise estimate of effect and explaining inconsistencies among studies. By combining information over different studies, an integrated analysis will have more statistical power to detect an effect than an analysis based on only one study. By providing a more precise estimate of the effect, a meta-analysis will provide stronger evidence than that derived from any individual study. Since childhood leukemia is a relatively rare disease, sample sizes of some previous studies have been small and the risk estimates have lacked precision[20,23,25] – ideal circumstances in which to employ meta-analysis. Moreover, a meta-analysis will enable not only a quantitative integration of results but also an exploration of why studies may have disparate results. The latter can often be as important as, or more important than, the summary measure.

Second, a meta-analysis will advance scientific knowledge by clarifying the

* After the initial writing and approval of this present study, a meta-analysis examining birth weight as a risk factor for childhood leukemia was published in October 2003 by Hjalgrim and colleagues. [94]

role of high birth weight in childhood acute leukemia. As noted by a recent report summarizing a NIH workshop on childhood cancer, the causes and risk factors of childhood malignancies are poorly understood despite numerous epidemiological studies over several decades.[36]

Third, findings from a meta-analysis could influence clinical practice and public health policy. Assuming that a positive association between high birth weight and acute leukemia is confirmed, clinicians may consider changes in their recommendations given to female patients regarding those factors which could influence high birth weight in their babies.

Several factors are known to correlate with high birth weight. These correlates include gestational diabetes[43], maternal obesity[44], maternal weight gain,[45-47] maternal and paternal birth weights,[48, 49] estrogen levels in pregnancy[50], low maternal serum alpha-fetoprotein levels,[51] and smoking during pregnancy.[52] In addition, birth weight varies directly with levels of insulin-like growth factor 1 (IGF-1) and leptin in cord blood.[53]

Many of these determinants of high birth weight cannot be changed or treated. Some however, such as weight gain during pregnancy, is potentially amenable to change. Greater weight gain during pregnancy is associated with higher birth weights. One study reported that women who gained 24-33 pounds and over 33 pounds during pregnancy had 1.77 times and 2.86 times the risk, respectively, of having a heavy baby (> 4000 grams) than women who gained less than 14.9 pounds.[54] Therefore, interventions that lead to optimal weight gain may play an important role in reducing the prevalence of high birth weight babies

and thus, reduce the risk of acute leukemia. The importance of periodic prenatal weight monitoring of women may also be underscored.

In 1990, the Institute of Medicine (IOM) published a recommendation to base total weight gain and pattern of gain on pre-pregnancy body mass index (BMI), as shown in Table 3.[55] Current IOM recommendations for optimal weight gain may place women who follow these recommendations at higher risk for having high birth weight babies.[54] Confirming the link between high birth weight and acute leukemia may warrant careful review of weight gain recommendations for pregnancy.

Table 3. Recommended Total Weight Gain Ranges for Pregnant Women, by Pre-pregnancy Body Mass Index (BMI) [55]

		Assumed distribution of weight gain	
Pre-pregnancy weight-for-height category	Total weight gain (lbs)	First trimester (lbs)	Second & third trimesters (lbs/wk)
Low (BMI <19.8)	28-40	5.0	1.1
Normal (BMI 19.8-26)	25-35	3.5	1.0
High (BMI > 26-29)	15-25	2.0	0.7

Not only does total weight gain during pregnancy correlate with birth weight, but also the timing during pregnancy of weight gain is critical. Studies have pointed to the importance of second trimester rate of gain in determining birth weight.[45,46,56] For example, one study showed that low weight gain in the first and second or in the second and third trimesters were associated with significant decreases in birth weight whereas no important change in birth weight was seen for low gain in the first and third trimesters.[56]

If high birth weight is indeed a risk factor for childhood acute leukemia rather than a result of confounding or bias, what will be the impact of reducing birth weight on the incidence of ALL? According to the National Center for Health Statistics (NCHS), about 9.4 percent of children born in the United States in 2001 had high birth weight (> 4,000 grams).[57] Table 4 shows the percent of high birth weight babies and the mean birth weight from 1970 to 2001 based on national data published by NCHS.[58-69] The proportion of high birth weight babies has generally trended downward after peaking at about 11 percent in the mid-1980s.[58] As noted earlier, studies that have found an association between ALL and high birth weight report odds ratio ranging from 1.4 to 2.5. Assuming a risk (r) of 1.4 and 9.4% as the proportion (p) of children with high birth weight, the population attributable risk (PAR) is 3.6% using the following formula:[70]

Table 4. Percent of babies born with high birth weight (HBW) and mean birth weight (in grams), United States, 1970-2001

Year	Percent HBW (> 4,000 grams)	Mean BW (standard deviation)
1970	8.4%	
1975	9.4%	
1980	10.7%	
1985	11.1%	
1990	10.9 %	3,365 (583)
1991	10.6 %	
1992	10.7 %	
1993	10.5 %	
1994	10.4 %	
1995	10.3 %	3,353 (581)
1996	10.2 %	
1997	10.1 %	
1998	10.1 %	
1999	9.9 %	
2000	9.9 %	3,339 (573)
2001	9.4 %	

$$PAR = [p (r-1)] / [p (r-1)+1]$$

Assuming a relative risk of 2.5, the attributable risk becomes 12.4%. In other

words, approximately 3.6% to 12.4% of ALL in children may be attributable to high birth weight, and presumably could be prevented by decreasing birth weight. High birth weight is associated with other malignancies such as Wilms' tumor and neuroblastoma, as well. [27,57] Therefore, the impact of decreasing birth weight may go beyond acute leukemia.

Fourth, a detailed exploration of the reported association between high birth weight and childhood acute leukemia could highlight gaps in the literature and provide insight into new directions for research. For example, the specific biologic mechanism of action for such an association is currently unclear. Several pathways are possible.

One explanation is that high birth weight plays a causal role in the development of acute leukemia. For example, Westergaard et al postulated that an increased volume of precursor cells results from high birth weight.[26] This theory of a link between organ mass, number of cells, and cancer risk has been suggested regarding other cancers (e.g., brain tumors in children[71] and breast cancer[72]). Increasing birth weight may also be associated with higher rates of cell division,[20] which might be associated with an increased risk of cancer. Still other possibilities include high birth weight affecting the production of insulin-like growth factors that, in turn, may stimulate the growth of lymphoid and myeloid cells.[73]

Alternatively, high birth weight may be acting as a surrogate marker, and not part of the causal pathway. For example, high birth weight could act as a proxy for *in utero* exposures that have a causal association, such as genetic mutations

or pre-malignant cell changes. Shu et al. hypothesized that *in utero* exposure to high endogenous estrogen levels, a predictor of birth weight,[74] is involved in the etiology of childhood ALL.[22] Still another explanation might be that children with a high birth weight are more likely to be exposed to diagnostic radiation *in utero* so that this radiation exposure accounts for the elevated risk of acute leukemia associated with high birth weight.[29]

Etiologic mechanisms of cancer are complex and are likely to be multi-factorial.[75] Judgments about causality from epidemiologic data extend beyond the validity of results of any single study and must take into consideration many criteria. These criteria include temporal sequence, strength of the association, biologic plausibility, consistency of the findings, the presence of a dose-response relationship, among others.[76]

Fifth, a meta-analysis will provide a comparison for a pooled analysis currently underway by Dr. Forman and others. A pooled analysis of individual patient level data from different studies has some advantages over a meta-analysis including the ability to adjust for the same confounders using the same statistical model. However, it is more expensive, time-consuming, and requires the willingness of investigators to provide data for inclusion in the pooled study. Few studies have examined how pooled analysis and meta-analysis on the same topic compare.

In short, given (1) the import of acute leukemia as a cause of cancer in children, (2) the overall lack of identified risk factors for ALL and AML, and (3) the inconsistent evidence concerning the association between high birth weight and

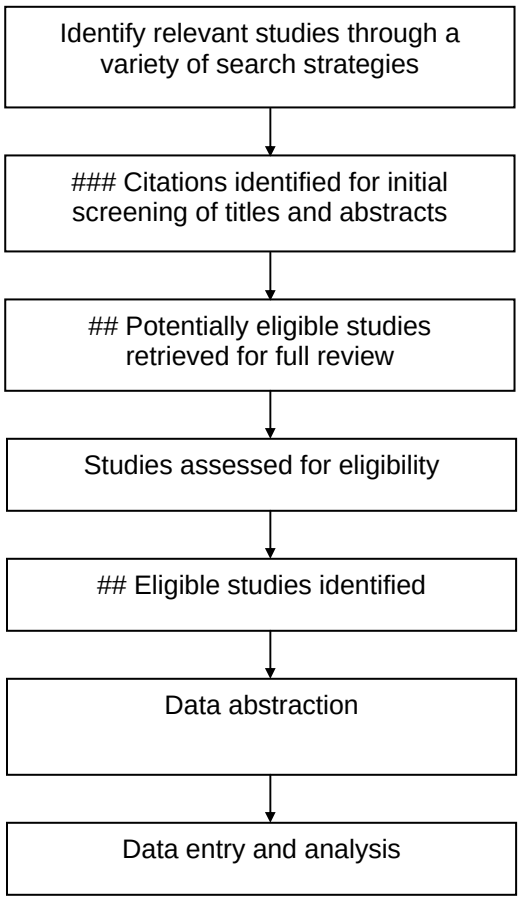
childhood acute leukemia, the significance of conducting a meta-analysis lies in its potential to clarify the mixed evidence, guide clinical practice and public health policy, suggest direction for future research, and provide a comparison for a pooled analysis addressing the same issue.

2. METHODS

2.1 Identification and Selection of Studies

The consensus statement and guidelines published by Stoup et. al. for the meta-analysis of observational studies in epidemiology was followed in the design, performance, and reporting of this meta-analysis.[77] To identify relevant studies, I will search journals, book chapters, abstracts, dissertations, and conference proceedings using the following databases: MEDLINE (National Library of Medicine) from 1966 through March 2004, Current Contents (Institute for Scientific Information) from 1990 to March 2004, EMBASE (Elsevier Science) from 1974 through March 2004, BIOSIS (Biological Abstracts Inc.) from 1976 through March 2004, and Dissertation Abstracts Online (University Microfilms International) from 1962 through March 2004. Except for the latter database, all searches used the medical subject heading terms [“acute leukemia”] and [“child”] and [“risk factors” or “birth weight”]. Dissertation Abstracts Online does not permit searches by subject terms, only by title terms. Therefore, the search of this database used the title terms [“acute leukemia”] and [“child”]. In addition to these five databases, a manual search of references cited in all eligible studies was performed to detect additional eligible publications. Reports published in both English and non-English were included, with the latter translated into English by a computer service and edited by a translator. All searches were limited to studies of human subjects and to those that were published (defined as material that is printed and available to the public). Identification of unpublished studies is most realistic when studies are registered in their planning stages or when they

Figure 3. Flowchart of Methodological Steps



begin. Although several registries of clinical trials exist, registers of non-experimental studies have not yet been created. Therefore, while retrieval of information from all studies, not just published ones is ideal, it was not feasible in this instance.

Figure 3 outlines a flowchart of methodological steps that was followed to identify and find studies. The search strategies described above were employed to identify relevant citations. The titles and abstracts of each citation were then screened for those studies that examined birth weight as a risk factor and leukemia as an outcome among a pediatric population. These potentially eligible studies were then retrieved for full review. Two investigators (Taylor and Lipnick) independently reviewed all potentially eligible studies and determined study eligibility using a standardized form (see Appendix A). The inter-observer agreement (i.e., kappa statistic) was calculated and disagreements were resolved by discussion or by a third reviewer, when necessary.

Inclusion will be restricted to the following criteria: (1) a case-control or cohort design, (2) a pediatric study population (< 18 year-old), and (3) studies that reported the relative risk (or odds ratio) of leukemia, ALL or AML associated with high birth weight (> 4000 grams), or that provide data in which the relative risk (or odds ratio) could be calculated. We maintained a log of ineligible studies, documenting the reasons why a study was deemed ineligible. No attempt was made to contact authors to obtain missing data.

Since study results of individual studies are already known through the literature search and screening of titles and abstracts, masking was not feasible. In assessing eligibility, it was sometimes necessary to read the results to determine whether the inclusion criteria were met, again making masking impractical. However, since the inclusion criteria are relatively unambiguous, it is unlikely that the lack of masking would induce bias.[78]

In cases in which there is more than one published report on the same population or group of patients the most recent or most complete article was selected for analysis. To minimize selection bias, no study was rejected because of methodological characteristics or any quality criteria. However, study method and quality were assessed and included in sensitivity analyses to determine whether these have an effect on our meta-analysis results.

2.2 Data Abstraction

To reduce bias, two investigators (Taylor and Lipnick) independently conducted data abstraction using a standardized data collection form (see Appendix B). The inter-observer agreement was calculated and disagreements

were resolved by discussion or by a third reviewer, when necessary.

2.3 Data Analyses

Relative risks were used as a measure of the relation between high birth weight and the risk of ALL and of high birth weight and the risk of AML. For case-control studies, the odds ratio was used as a surrogate measure of the corresponding relative risk. Because the absolute risk of ALL and AML is low (i.e., disease is rare), the odds ratio approximates the relative risk.[70] The outcomes considered were ALL, AML, and leukemia combined (for studies that did not differentiate among leukemia types). Both the incidence of these outcome variables and mortality due to these variables were considered. Data analysis involved five components: evaluating heterogeneity, combining results across studies, assessing potential publication bias, assessing study quality, and conducting sensitivity and subgroup analyses.

2.3.1 Evaluation of Heterogeneity

First, the statistical heterogeneity of the findings of the individual studies was evaluated. Statistical heterogeneity or variation is the degree to which results of studies included in a meta-analysis are different.[37] Tests of heterogeneity assess whether any observed variability in study results is greater than that expected to occur by chance and therefore, the extent to which the studies are similar enough to warrant summarization of results. [37]

Tests of heterogeneity follow the general pattern of testing the sum of the weighted difference between the summary effect measure and the measure of

effect from each study. The statistic calculated was the chi-square distribution, usually called Q. The number of degrees of freedom (df) of Q is equal to the number of studies minus one. The estimates of effect were tested for heterogeneity using Wolfe's method.[79] Relative risks from individual studies first were transformed to their natural logarithms, or ln (RR_i), to stabilize the variances and to normalize the distributions. The heterogeneity of ln (RR_i) across the k studies was then be computed using Wolfe's chi-square test:

$$\text{Chi-square} = \text{sum}\,[\text{weight}_i \times (\ln RR_i - \ln RR_{Wolfe})^2], \text{ with df} = k-1$$

$$\text{where } \ln RR_{Wolfe} = \text{sum}\,(\text{weight}_i \times \ln RR_i) \quad \text{sum weight}_i$$

$$\text{weight}_i = 1/\text{variance}_i$$

where w_i is a weight that consists of the inverse of the variance of the ln RR_i.

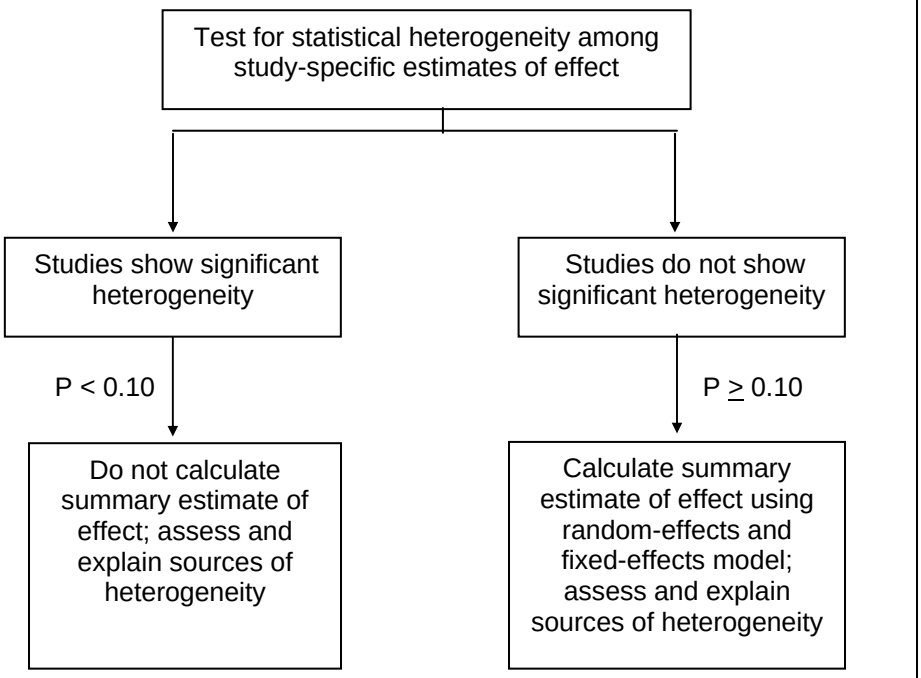
When the p value for the test of heterogeneity exceeded a critical value of alpha (i.e., 0.10), the hypothesis of heterogeneity was rejected. In this instance, we concluded that the studies are homogeneous – that is – the studies are measuring an effect of the same size. A two-tailed p value of less than 0.10 indicated statistical significance. Because statistical tests for heterogeneity are insensitive, visual inspection of the data, using funnel plots and Galbraith plots also were performed. Data management and analysis were performed using STATA software (version 8).

Second, whether the data can be combined was decided after calculating the heterogeneity of the study results (Figure 4). If heterogeneity is significant,

then results were not combined in order to guard against burying important inconsistencies in statistical aggregations.[37] Rather, the focus was on assessing sources of the heterogeneity and on resolving the apparent lack of agreement among the individual studies.[80,81]

On the other hand, if heterogeneity across all studies is not significant, a weighted average of the summary estimate of effect was calculated. Depending upon the statistical degree of heterogeneity present, we combined results using either a random effects model or a fixed-effects model. (If studies are homogeneous, then the choice between the fixed-effects model and the random-effects model is unimportant, as the models will yield results that are identical.[37]) Because the statistical power of tests of heterogeneity is low, the absence of statistical evidence of heterogeneity did not preclude an assessment of the possible sources of clinical heterogeneity.

Figure 4. Flowchart of approach for combining results



2.3.2 Combining Results

If heterogeneity is not significant, the data were combined to get a summary estimate of effect and its 95 percent confidence interval. The effect of high birth weight on risk of ALL and of AML was estimated by calculating an average relative risk weighted by the variability of the estimate reported in each study. As noted above, there are two types of methods for combining estimates of effect from eligible studies, fixed effects model (e.g., Wolfe's method)[79] and a random effects model (e.g., DerSimonian and Laird method).[82] Decisions concerning which to use were made on the basis of study heterogeneity, as outlined in Figure 4. Meta-analysis without significant evidence of heterogeneity used a fixed effect model while a random effects model was used when study heterogeneity

was of concern. A two-tailed p value of less than 0.05 indicated statistical significance.

For the fixed effects model, Wolfe's method (also known as the inverse variance method) was utilized. The summary RR_{Wolfe} and 95% confidence interval (CI) using Wolfe's method was computed with the following formulas and then exponentiated:

$$\ln RR_{Wolfe} = \text{sum}(\text{weight}_i \times \ln RR_i) \quad \text{sum weight}_i$$

$$\ln RR_{Wolfe\text{-}95\%\ CI} = \ln RR_{Wolfe} \pm 1.96\ (1/\sqrt{\text{sum weight}_i})$$

$$\text{weight}_i = 1/\text{variance}_i$$

Likewise, for the random effects model, the summary $\ln RR_{DL}$ and 95% CI using DerSimonian and Laird method was computed using the following formula and then exponentiated:

$$\ln RR_{DL} = \text{sum}(\text{weight}_i^* \times \ln RR_i) \quad \text{sum weight}_i^*$$

$$\ln RR_{DL\text{-}95\%\ CI} = \ln RR_{DL} \pm 1.96(1/\sqrt{\text{sum weight}_i^*})$$

$$\text{where weight}^* = 1 / [D + (1 / \text{weight}_i)] \text{ and}$$

$$\text{weight}_i = 1 / \text{variance}_i$$

where variance_i for each study is estimated using the Wolfe method and where D was calculated using a standard formula.[37]

Under a fixed-effects model (e.g., Wolfe's method), the between-study variance is ignored in computing the study weights and only the within-study variance is considered.[37] Under the random effects model (e.g., Dersimonian and Laird method), both between- and within-study variation determine the weight.[37] Fixed-effects models assume that an exposure has a single true effect, whereas

random-effects models assume that an effect may vary across studies. The fixed effects model assumes that all of the individual studies are similar in that they share the same underlying exposure effect on outcome. Consequently, the observed differences in their results are considered to be due to chance alone (sampling error within each study). The random effects model assumes that each study estimates a unique exposure effect that, even given a large amount of data, might still differ from the effect in another study.

Weights in a fixed effects model are largely determined by the size of the individual studies, with large studies contributing more to the combined estimate than small studies.[83] In a random effects model, as the between studies variance grows, this will diminish the weights based upon the within study differences and thus, large and small studies will tend to be weighted equally. [83] Said a different way, the random effects model results in relatively more weight being given to smaller studies than the fixed effect model.[83]

The random effects model is equivalent to the fixed effects model when there is no difference in the exposure effect between different studies.[37] In general, using a random effects model results in larger variance and confidence intervals than a fixed effects model because a between-study component is added to the variance.[37] While the random effects model allows for non-homogeneity between the effects of different studies, it does not eliminate nor explain this variation.[37]

Only one estimate of effect from each eligible study was used in the calculation of the summary estimate of effect because using more than one

would inappropriately give greater weight to studies with more than one estimate of effect. Unadjusted estimates of effect and adjusted estimates of effect were combined separately. When an individual study reported more than one adjusted estimate of effect, we chose the “most adjusted” estimate; that is, the estimate with the largest number of variables in the model as this is likely to be the least confounded estimate.

2.3.3 Assessment of Potential Publication Bias

The possibility of publication bias was assessed by both visual and statistical tests. Visual assessment was done by constructing a funnel plot, a simple scatter plot in which log relative risk is depicted on the horizontal axis and some measure of the sample size (e.g., variance or standard error) on the vertical axis.[84] In the absence of publication bias, because of sampling variability, the plot should resemble a funnel with the large opening down and the tip pointed up, with study results centered on the true effect size and the degree of scatter decreasing with sample size.[84] Precision in the estimation of the underlying exposure effect will increase as the sample size of component studies increases. If there is bias against the publication of null results or results showing a negative effect of exposure, the left corner of the pyramidal part of the funnel will be distorted or missing.[84] Although not definitive, when a funnel plot is distorted, publication bias is suspected.

The statistical assessment for the presence of publication bias included both the Begg’s rank sum and the Egger’s tests. The Begg’s rank sum test is the statistical analogue of the graphical approach of the funnel plot.[85] It examines the

association between the effect estimates and their variances.[85] The Egger's test is based on doing a linear regression of the standardized estimates of effect against their precision (1/variance).[86] The 95% confidence intervals of the regression line's y intercept should include zero in the absence of publication bias.[86]

The sensitivity of results to possible unpublished studies was assessed using two methods, a "file drawer" test and the Duval-Tweedy trim and fill method. The file drawer test estimates the number of unpublished null studies (RR=1.0) that would need to exist to negate the results of the published studies that were included in the meta-analysis.[87]

The Duval-Tweedy trim and fill method assesses the funnel plot for asymmetry.[83] If asymmetry is found, unbalanced studies are iteratively trimmed until the residual plot is symmetric. The unbalanced studies are then reentered into the analysis, with studies of equal weight but opposite effect -- that is the "missing" studies that would make the plot symmetric are filled in, and a new summary effect is calculated. [83]

2.3.4. Assessment of Study Quality

Not all studies included in a meta-analysis are likely to be equal in quality of design, method, or conduct. Study quality was assessed through describing certain reported factors (e.g., sample size, percent participation rate, how birth weight was ascertained [from interview or registry data], whether leukemia incidence or mortality was examined, whether there was control for confounding, and whether the study was peer reviewed). Differences in study quality were

taken into account through sensitivity and subgroup analysis (as described in the next section). No quality scores were generated nor were quality scores used to perform weighted analysis (where the relative weight of an individual study in a meta-analysis is determined by the magnitude of the quality score). Several reasons bolstered this decision.

First, a consensus statement on the meta-analysis of observational studies recommends subgroup or sensitivity analysis rather than using quality scores as weights in the analysis to account for study quality, due to the subjective nature of the latter.[77]

Second, assigning relative values to specific study methods to generate a quality score is largely an arbitrary and subjective process. For example, what defines “adequate” when evaluating “selection description” or “appropriate” when evaluating “statistical analysis”? Furthermore, rating different sources of bias in relation to one another is inherently difficult. For instance, is recall bias worse than diagnostic bias? How much worse is information bias than uncontrolled confounding?

Third, quality rating is generally based on information that is reported, which may not be an accurate measure of the truth about an element of quality. For example, if a study does not state that the investigators were blinded to outcome, it does not necessarily mean that the study was not blinded. Short of contacting the author(s), truth may not be elucidated from what is reported. Conversely, a study may suffer from bias, but evidence of the bias may not be detectable in the study report.

Fourth, the reliability and validity of the quality rating scales have not been well evaluated. Empiric study reveals large disparities in the development of scales and checklists to assess quality.[88] The assumption of a direct relation between study quality and results may be unfounded. For example, when one group of investigators applied a certain quality scale to studies reviewed in seven meta-analyses, no association between quality scores and study results was demonstrated.[89] Moreover, to date, only three methodological features have been empirically shown to influence the results of studies about therapy: randomization, allocation concealment, and masking.[90-93] The first two of these criteria do not pertain to non-experimental studies. In addition, while standard instruments and checklists to evaluate study quality have been developed for randomized control trials, none have been developed and validated for non-experimental studies.

In short, the standardized assessment of study quality, especially as it pertains to non-experimental studies, is a sub-field of meta-analysis that is still in its infancy. Therefore, given the theoretical and practical problems of assessing study quality and using quality scores as a weighting variable, key components of study design and methodology were examined through sensitivity and subgroup analyses instead.

2.3.5 Sensitivity and Subgroup Analyses

Sensitivity analysis tests the robustness of the overall findings of the meta-analysis with respect to different assumptions or inclusion of certain studies.[37] It is an important tool for investigating heterogeneity. The influence of individual

studies was assessed by estimating the summary estimate of effect in the absence of each study. When the exclusion of an individual study produced significant changes to the overall estimate of effect, the individual study was investigated for reasons why (e.g., study design, geographic location of study, etc.)

Subgroup analysis, a form of sensitivity analysis, involves calculating a summary estimate for subgroups of studies to investigate variations of the estimate of effect. Heterogeneity was examined by classifying studies according to potential sources of variation and analyzing these subgroups of studies with different designs (i.e., case-control versus cohort) and characteristics (e.g., language of publication, peer reviewed status, studies that controlled for possible confounders, studies in which investigators were masked, etc.) for important differences. Heterogeneity was explored through a combination of stratified analyses and meta-regression. As in any regression analysis, meta-regressions attempt to identify significant associations between the outcome (dependent variable) and covariates of interest (independent variables). Whereas in observational studies, the unit of analysis is the individual patient, in meta-regressions the unit of analysis is the study or subgroup.

To evaluate whether age is an interacting factor in the possible relationship between high birth weight and ALL or AML, we conducted subgroup analysis and compared summary estimates of effect among studies that report age-specific estimates of effect.

3. RESULTS

3.1 Literature Search

To identify relevant studies, five databases: Medline, Biosis, Current Contents, Embase, and Dissertation Abstracts were searched using the medical subject heading terms [“acute leukemia”] and [“child”] and [“risk factors” or “birth weight”]. Dissertation Abstracts does not permit searches by subject terms, only by title terms. Therefore, the search of this database used the title terms [“acute leukemia”] and [“child”]. In addition to these five databases, a manual search of references cited in all eligible studies was performed to detect additional eligible publications. While Medline alone provided 1,331 (79%) citations, 354 (21%) additional unique citations were provided by other sources (Figure 5). Results reported in Figure 5 were derived in the following manner: (1) Results from all the data sources were compared first to Medline; any duplicate citations were assigned to Medline. (2) Results from Current Contents, Embase, Dissertation Abstracts and references cited in studies were compared next to Biosis; any duplicate citations were assigned to Biosis. (3) Results from Embase, Dissertation Abstracts and references cited in studies were compared next to Current Contents; any duplicate citations were assigned to Current Contents. (4) Results from Dissertation Abstracts and references cited in studies were compared to Embase; any duplicate citations were assigned to Embase. (5) References cited in studies were compared to Dissertation Abstracts; any duplicate citations were assigned to Dissertation Abstracts.

Figure 6 shows the results of the overall search strategy employed. From a review of 1,685 unique abstracts identified in the database search and reference lists of articles, 44 articles were selected for a full review because their abstracts contained the words of the medical subject heading terms listed above. Of these 44 studies, 13 met the eligibility criteria while the remaining 31 were excluded for a variety of reasons (Table 5). Eleven studies used an outcome that was too broad (e.g., childhood cancer, cancer, leukemia, lymphatic leukemia, and myeloid leukemia), seven reported insufficient data (i.e., information on estimates of effect were not provided or could not be calculated), six used a different cutoff for high birth weight, four were study designs other than a case-control or cohort, and four overlapped with other included studies. One study[117] was included for its AML cases only – ALL cases were excluded because of their overlap with another study[22]. Thus, the main meta-analysis included 13 studies that met the inclusion criteria – that is, had the following criteria: (1) a case-control or cohort design, (2) a pediatric study population (<18 year-old), (3) studies that reported the relative risk (or odds ratio) of ALL, AML, or acute leukemia associated with high birth weight (>4000 grams), or that provide data in which the relative risk (or odds ratio) could be calculated, and (4) listed in one of five databases or from the references cited in the eligible studies.

While 13 studies strictly met the inclusion criteria, additional analyses were performed to explore changes to results when these criteria (namely >4,000 g as the cutoff for high birth weight) are loosened. These additional analyses are discussed in section 3.6.

Figure 5. Identification of Publications

Source	Unique citations
Medline	1331
Biosis	87
Current Contents	31
Embase	192
Dissertation Abstracts	38
References cited in studies	6
Total	1685

Searched on medical subject heading terms [“acute leukemia”] and [“child”] and [“risk factors” or “birth weight”]

Figure 6. Results of Search Strategy

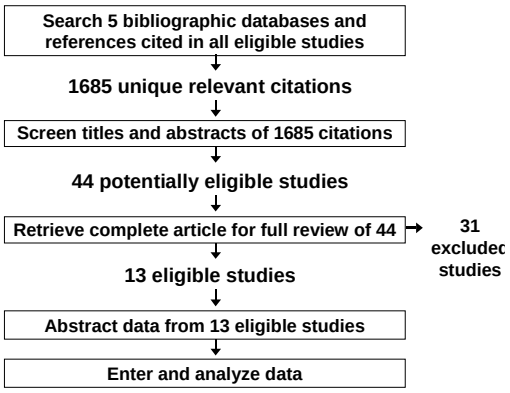


Table 5. Studies Excluded from the Main Meta-Analysis

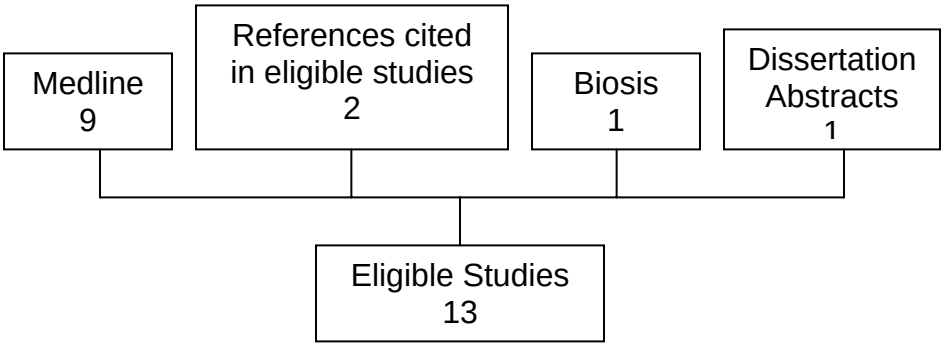
Author (reference no.)	Publication year	Country	Outcome	Study type	Comment
Reason for exclusion: study design other than case-control or cohort					
Salvesen KA (95)	1999	NA	Cancer	Review	
Severson RK (96)	1999	NA	Acute leukemia	Review	
Neglia JP (97)	1988	NA	Acute leukemia	Review	
Reason for exclusion: Outcome too broad					
Sorahan T (104)	2001	U.K.	Childhood cancers	Case-control	
Smulevich VB (105)	1999	Russia	Childhood cancers	Case-control	
Hirayama T (99)	1980	Japan	Cancer	Case-control	
Daling JR (29)	1984	U.S.	Cancer, leukemia	Case-control	
Fasal E (30)	1971	U.S.	Leukemia	Case-control	HBW defined as $\geq$ 8.5 lbs (3856 g)
MacMahon B (102)	1962	U.S.	Leukemia	Case-control	HBW defined as $\geq$ 8.5 lbs (3856 g)
Jackson EW (106)	1968	U.S.	Leukemia	Cohort	Relative risk not provided or could not be calculated
Uderzo C (110)	1996	Italy	Leukemia	Case-control	Odds ratio not provided or could not be calculated
Shaw G (111)	1984	U.S.	Leukemia	Case-control	Odds ratio not provided or could not be calculated
Fajardo-Gutierrez A (103)	1993	Mexico	Leukemia	Case-control	HBW defined as > 3500 g
Zack M (34)	1991	Sweden	Lymphatic leukemia, myeloid leukemia	Case-control	Odds ratio not provided or could not be calculated
Reason for exclusion: duplication of another eligible study					
Robison LL (32)	1987	U.S.	ALL	Case-control	Duplication of Kaye (14)
Buckley JD (31)	1994	U.S.	ALL	Case-control	Duplication of Yeazel (27)
Shu (117) *	1999	U.S.	ALL, AML	Case-control	Only ALL cases are excluded because duplication of Shu (22)
Ross JA (23)	1997	U.S.	ALL, AML	Case-control	Duplication of Shu (22) for ALL cases and Shu (118) for AML cases
Reason for exclusion: different cutoff for high birth weight (HBW)					
Westergaard T (26)	1997	Denmark	ALL, AML	Cohort	HBW defined as $\geq$ 4010 g
Murray L (21)	2002	N. Ireland	ALL	Cohort	HBW defined as $\geq$ 3500 g
McKinney PA (100)	1999	Scotland	ALL	Case-control	HBW defined as $\geq$ 3500 g
Shu XO (101)	1994	China	Acute leukemia	Case-control	HBW defined as > 3700 g
Shu XO (17)	1988	China	ALL	Case-control	HBW defined as $\geq$ 3500 g
Roman E (35)	1997	U.K.	ALL, AML	Case-control	HBW defined as > 3500 g
Reason for exclusion: insufficient data					
Suminoe A (98)	1999	Japan	ALL, AML	Case-control	Odds ratio not provided or could not be calculated
Infante-Rivard C (107)	2003	Canada	ALL	Case-control	Odds ratio not provided or could not be calculated
Cocco P (108)	1996	Italy	ALL	Case-control	Odds ratio not provided or could not be calculated
Dockerty JD (109)	2001	U.K.	ALL	Case-control	Odds ratio not provided or could not be calculated
Wertelecki W (25)	1973	U.S.	ALL	Case-control	Odds ratio not provided or could not be calculated
Cnattingius S (112)	1995	Sweden	Myeloid leukemia	Case-control	Odds ratio not provided or could not be calculated
Pombo-de-Oliveira MS (113)	2003	Brazil	Acute leukemia	Case-control	Odds ratio not provided or could not be calculated

* The AML cases of this study were included as eligible

3.2 Description of Included Studies

Figure 7 shows the database source of the 13 studies included in the main meta-analysis. Without searching beyond Medline, four (31%) studies would have been missed.

Figure 7. Database source of 13 studies included in meta-analysis



Tables 6A, 6B, 6C, and 6D describe the 13 studies included in the main meta-analysis. All of the studies were case-control studies published between 1991 and 2004. They included 8,795 children with acute leukemia (6,287 with ALL, 706 with AML, and 1,802 with acute leukemia unspecified [for studies that did not differentiate among leukemia types]), and a total of 16,232 controls (12,362 for ALL, 1,921 for AML, and 1,949 for acute leukemia unspecified. All studies examined the incidence of disease. All studies were reported in English. With a few exceptions, the age span of cases was similar across studies. Reynolds[33] and Okcu[20] included only children aged < 5 years. Three studies had an upper age limit of 18 years.[14, 27, 117] The majority of studies (eight of 13) were conducted in the United States while two studies were conducted in Germany, and one study each was done in Sweden, France, and Greece. All studies

performed either matching or adjustment or both for a variety of potential confounders. While high birth weight was defined as >4,000 g in all of the studies (per inclusion criteria), the reference or comparison birth weight varied among individual studies. Reference birth weights used among the 13 studies included approximately <3000 g, 2500-3500 g, 2500-4000 g, 3000-3499 g, 3010-3509 g, < 3500 g, and ≤4000 g.

Table 6A. Characteristics of Studies Included in the Main Meta-Analysis

Author (reference no.)	Publication year	Database source*	Case recruitment period	Country	Study type	Cases (no.)	Controls (no.)	Age range (yrs)
Acute lymphoblastic leukemia								
Shu XO (22)	2002	B	1989-1993	United States	Case-control	1839	1985	< 15
Jourdan-Da Silva N (114)	2004	M	1995-1998	France	Case-control	408	567	< 15
Reynolds P (33)	2002	M	1988-1997	United States	Case-control	1407	2811	< 5
Okcu MF (20)	2002	M	1995	United States	Case-control	83	830	< 5
Kaye SA (14)	1991	M	1969-1988	United States	Case-control	337	1336	< 18
Cnattingius S (24)	1995	M	1973-1989	Sweden	Case-control	610	3061	< 16
Savitz DA (115)	1994	R	1976-1983	United States	Case-control	68	208	< 15
Rosenbaum PF (116)	1998	D	1980-1991	United States	Case-control	251	748	< 15
Yeazel MW (27)	1997	M	1982-1989	United States	Case-control	1284	816	< 18
Acute myeloid leukemia								
Shu XO (117)	1999	R	1989-1993	United States	Case-control	456	538	< 18
Yeazel MW (27)	1997	M	1982-1989	United States	Case-control	185	816	< 18
Jourdan-Da Silva N (114)	2004	M	1995-1998	France	Case-control	65	567	< 15
Acute leukemia unspecified								
Schuz J (15)	1999	M	1980-1997	Germany	Case-control	995	995	$\leq$ 15
Kaatsch P (118)	1998	M	1980-1994	Germany	Case-control	654	654	< 15
Petridou E (28)	1997	M	1993-1994	Greece	Case-control	153	300	< 15

* M=Medline, B=Biosis, D=Dissertation Abstracts, R=reference cited in eligible studies

Table 6B. Characteristics of Studies Included in the Main Meta-Analysis (continued)

Author (reference no.)	Outcome	Source of Cases	Source of Controls	Birth Weight Source	Case Response Rate	Control Response Rate	Matching Factors*	Adjusting Factors*
Acute lymphoblastic leukemia								
Shu XO (22)	ALL incidence	hospital records	community	interview	92%	77%	AD, G, R	MA, R, SES
Jourdan-Da Silva N (114)	ALL, AML incidence	cancer registry	population	interview	73%	71%	BD, G, S	AD, G, S
Reynolds P (33)	ALL incidence	cancer registry	population	registry	88%	100%	BD, S	GA
Okcu MF (20)	ALL incidence	cancer registry	population	registry	75%	100%	BD	BD, GA, MA, P, R, S, T
Kaye SA (14)	ALL incidence	hospital records	population	registry	43%	100%	BD	NR
Cnattingius S (24)	ALL incidence	hospital records	community	registry	100%	100%	BD, S	GA
Savitz DA (115)	ALL incidence	cancer registry	community	interview	68%	60%	G, S	NR
Rosenbaum PF (116)	ALL incidence	hospital records	community	interview	64%	49%	BD, R, S	BD, GA, MA, P, R, S, SES, SM
Yeazel MW (27)	ALL, AML incidence	hospital records	community	interview	50%	60%	NR	BO, GA, MA, S
Acute myeloid leukemia								
Shu XO (117)	AML incidence	hospital records	community	interview	83%	79%	AD, G, R	NR
Yeazel MW (27)	ALL, AML incidence	hospital records	community	interview	50%	60%	NR	BO, GA, MA, S
Jourdan-Da Silva N (114)	ALL, AML incidence	cancer registry	population	interview	73%	71%	BD, G, S	AD, G, S
Acute leukemia unspecified								
Schuz J (15)	Acute leukemia incidence	cancer registry	population	interview	81%	65%	AD, G, S	SES
Kaatsch P (118)	Acute leukemia incidence	cancer registry	community	interview	81%	67%	BD, G, S	SES
Petridou E (28)	Acute leukemia incidence	hospital records	hospital	interview	100%	98%	AD, G, S	NR

* AD, age at diagnosis; BO, birth order; BD, birth date; BP, birthplace; CP, calendar period; G, geographic location at diagnosis; GA, gestational age; MA, maternal age; NR, not relevant; P, Parity; R, race; S, sex; SES, socioeconomic status; SM, smoking; T, Tobacco use

Table 6C. Characteristics of Studies Included in the Main Meta-Analysis (continued)

Author (reference no.)	Ethnicity Data	High Birth Weight (HBW)	% HBW Cases	% HBW Controls
Acute lymphoblastic leukemia				
Shu XO (22)	Based on Mother: White 83.8% (cases), 88.9% (cntrols); Non-white 16.2% (cases), 11.1% (cntrols)	> 4000	15.1	12.3
Jourdan-Da Silva N (114)	Not reported	≥ 4000	10.2	6.7
Reynolds P (33)	White non-hispanic 38.4% (cases), 35.5% (cntrols); Black non-hispanic 2.7% (cases), 8.3 (cntrols); Hispanic 47% (cases), 44.4% (cntrols); Asian/Pacific Islander 10.9% (cases), 10.7% (cntrols); American Indian/other 0.6% (cases), 0.6% (cntrols); unknown 0.4% (cases), 0.4% (controls)	≥ 4000	13.5	12.5
Okcu MF (20)	Based on Mother: White 50.6% (cases), 45.1% (cntrols); Black 2.4% (cases), 12.5% (cntrols); Hispanic 45.8% (cases); 39.8% (controls); Other 1.2% (cases); 2.6% (controls)	> 4000	18.1	9.2
Kaye SA (14)	White 97.3% (cases) Non-white 2.7% (cases)	> 4000	Not reported	Not reported
Cnattingius S (24)	Not reported	≥ 4000	18.9	17.8
Savitz DA (115)	Not reported	> 4000	5.9	7.7
Rosenbaum PF (116)	White 96% (cases), 94% (controls); Non-white 4% (cases), 6% (controls)	≥ 4000	14.1	13.6
Yeazel MW (27)	For all cases of cancer, based on mother: White 84.8%; Black 4.2%; Hispanic 6.5%; Asian 1.5%; American Indian 0.7% Other 1.3%; Unknown 1%	> 4000	Not reported	Not reported
Acute myeloid leukemia				
Shu XO (117)	Based on mother: White 80.7% (cases), 84.4% (controls); Other 19.3% (cases), 15.6% (controls)	> 4000	12.7	13.9
Yeazel MW (27)	For all cases of cancer, based on mother: White 84.8%; Black 4.2%; Hispanic 6.5%; Asian 1.5%; American Indian 0.7% Other 1.3%; Unknown 1%	> 4000	Not reported	Not reported
Jourdan-Da Silva N (114)	Not reported	≥ 4000	4.8	6.7
Acute leukemia unspecified				
Schuz J (15)	Not reported	> 4000	13.1	10.3
Kaatsch P (118)	Not reported	> 4000	15.0	10.1
Petridou E (28)	Not reported	≥ 4000	12.4	8

Table 6D. Characteristics of Studies Included in the Main Meta-Analysis (continued)

Author (reference no.)	Reference Birth Weight (RBW)	% RBW Cases	% RBW Controls	Odds Ratio (95% CI)	Miscellaneous
Acute lymphoblastic leukemia					
Shu XO (22)	≤ 3000	17.7	18.9	1.40 (1.10-1.80)	Interval between diagnosis and interview for cases = 228 days; for controls= 292 days
Jourdan-Da Silva N (114)	3000-3499	40.8	39.2	1.40 (0.80-2.30)	Mean birth weight (standard deviation) 3322 (514) (cases), 3314 (522) (cntrols)
Reynolds P (33)	2500-3999	81.7	82.0	1.09 (0.90-1.31)	
Okcu MF (20)	2500-4000	80.7	83.9	2.20 (1.20-4.10)	Mean birth weight 3476 (cases), 3322 (controls); median 3515 (cases), 3345 (cntrols); range 2325-4621 (cases), 1021-5131 (cntrols)
Kaye SA (14)	≤ 4000	NR	NR	1.18 (0.84-1.67)	
Cnattingius S (24)	3000-3499	30.3	33.6	1.17 (0.91-1.51)	Reference group for birth weight selected to include group with largest number of control subjects in order to provide as stable estimates as possible
Savitz DA (115)	2500-4000	86.8	82.7	0.70 (0.20-2.30)	
Rosenbaum PF (116)	2500-3999	79.6	77.8	1.02 (0.67-1.54)	Mean birth weight 3497 (±552) (cases), 3403 (±604)(cntrols)
Yeazel MW (27)	≤ 4000	NR	NR	1.50 (1.10-1.90)	Mean birth weight (standard deviation) 3535 (1639) (cases); 3455 (1472) (cntrls); Median birth weight 3462 (cases); 3377 (controls)
Acute myeloid leukemia					
Shu XO (117)	< 3000	20.4	19.7	0.89 (0.57-1.38)	
Yeazel MW (27)	≤ 4000	NR	NR	1.50 ((1.00-2.40)	Mean birth weight (standard deviation) 3406 (560) (cases); 3455 (1472) (cntrls); Median birth weight 3348 (cases); 3377 (controls)
Jourdan-Da Silva N (114)	3000-3499	51.6	39.2	0.80 (0.20-2.80)	Mean birth weight (standard deviation) 3294 (396) (cases), 3314 (522) (cntrols)
Acute leukemia unspecified					
Schuz J (15)	2500-4000	82.0	86.7	1.40 (1.00-1.80)	
Kaatsch P (118)	2500-4000	80.9	86.9	1.64 (1.16-2.32)	
Petridou E (28)	2500-3999	85	85.7	1.57 (0.83-2.97)	

3.3 Main Meta-analysis and Evaluation of Heterogeneity

Figure 8, 10, and 11 show the study-specific odds ratios and the overall odds ratio of high birth weight associated with ALL, AML, and acute leukemia unspecified, respectively. While both fixed effects and random effects overall odds ratios are reported, the former is used when there is no statistical evidence of heterogeneity.

For ALL, the fixed effects overall odds ratio was 1.24 (95% CI: 1.12, 1.37; based on nine studies). In other words, a birth weight of > 4000 g. significantly increased the risk of developing ALL in children by 24% with a range of 12% to 37%. (The random effects overall odds ratio was 1.25 [95% CI: 1.11, 1.42; based on nine studies]). Except for one study,[115] all the odds ratios were greater than 1, but only three of the nine were statistically significant. The study by Savitz[115] found a negative association between birth weight and ALL (OR=0.70; 95% CI: 0.20, 2.30) and was the smallest study with 68 cases. This sample size has limited power to detect an association and limited precision leading to a wide confidence interval.

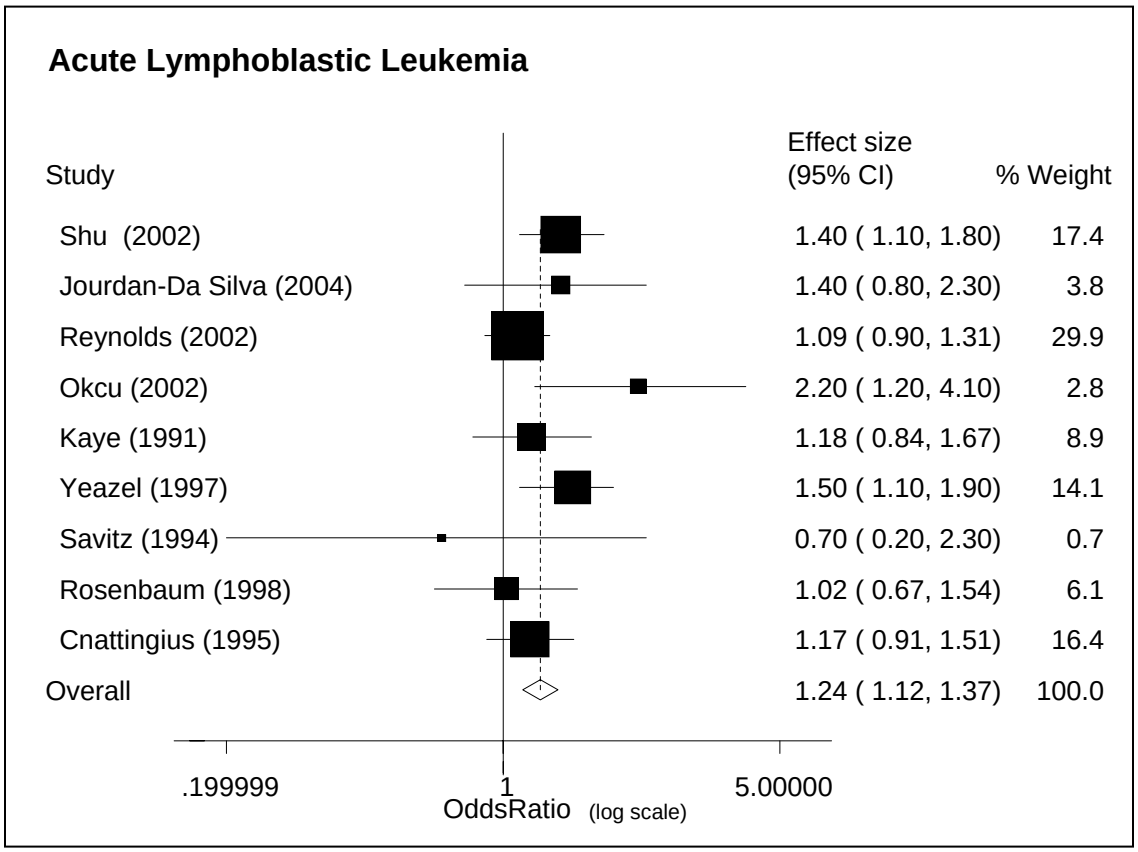
There is no statistical evidence of heterogeneity (Q statistic p=0.26) among the nine studies on ALL. Figure 9 provides a visual impression of the amount of heterogeneity by showing a Galbraith plot of the nine studies of ALL. For each study, the ratio of the odds ratio of ALL to its standard error is plotted against the reciprocal of the standard error. Therefore, the least precise results from small studies appear towards the left of the figure while the results from the largest studies towards the right. An overall log odds ratio is represented by the slope of

the regression line constrained through the origin, with its 95% confidence interval. The dotted lines are positioned two units above and below the solid line and depict and area within which, in the absence of statistical heterogeneity, 95% of the study results would be expected to lie. This graph indicates an absence of statistical heterogeneity in our meta-analysis as all of the studies lie within the confidence bounds.

Three studies provided sufficient information on AML and the effect of high birth weight as shown in Figure 10. For these studies, the fixed effects overall odds ratio was 1.14 (95% CI: 0.84, 1.54). While high birth weight increased the risk of developing AML by 14%, this association was not statistically significant. (The random effects overall odds ratio was 1.12 [(95% CI: 0.75, 1.68]). There was no statistical heterogeneity in these odds ratios across studies (Q statistic p=0.22).

Three studies provided sufficient information on acute leukemia unspecified and the effect of high birth weight as shown in Figure 11. For these studies, both the fixed effects overall odds ratio and the random effects overall odds ratio and their respective 95% CI were the same: 1.50 (95% CI: 1.22, 1.86). Therefore, high birth weight increased the risk of acute leukemia of unspecified type by 50% with a range of 22% to 86%. Although this association was statistically significant, it should be interpreted with caution as it is based on only three studies. There was no statistical heterogeneity in these odds ratios across studies (Q statistic p=0.78).

Figure 8. Odds ratios with corresponding 95% confidence intervals for ALL in children with high birth weight (≥4000 g)*



* For each study, the size of the boxes is proportional in area to the weight that the study has in calculating the summary odds ratio. Fixed effects summary odds ratios are displayed since there was no evidence of statistical heterogeneity across studies.

Figure 9. Galbraith Plot of Nine Case-Control Studies on High Birth Weight and the Risk of Childhood Acute Lymphoblastic Leukemia

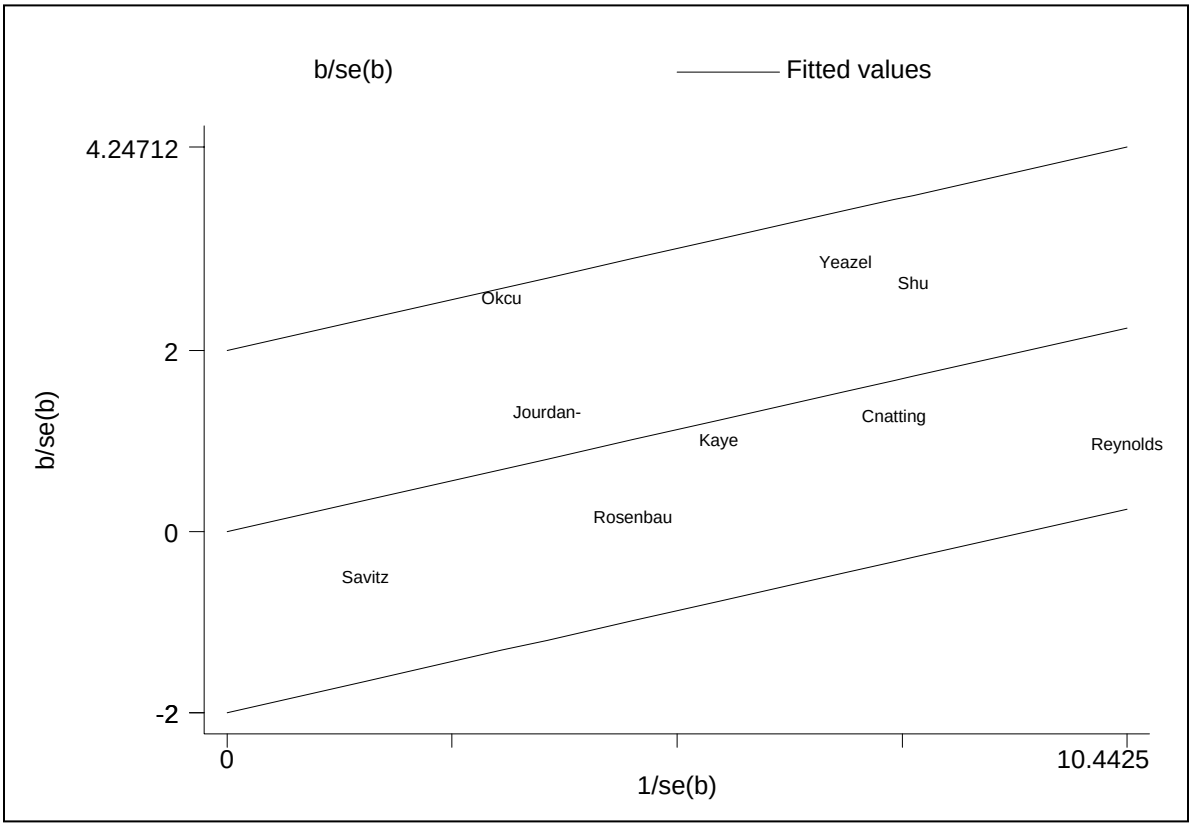
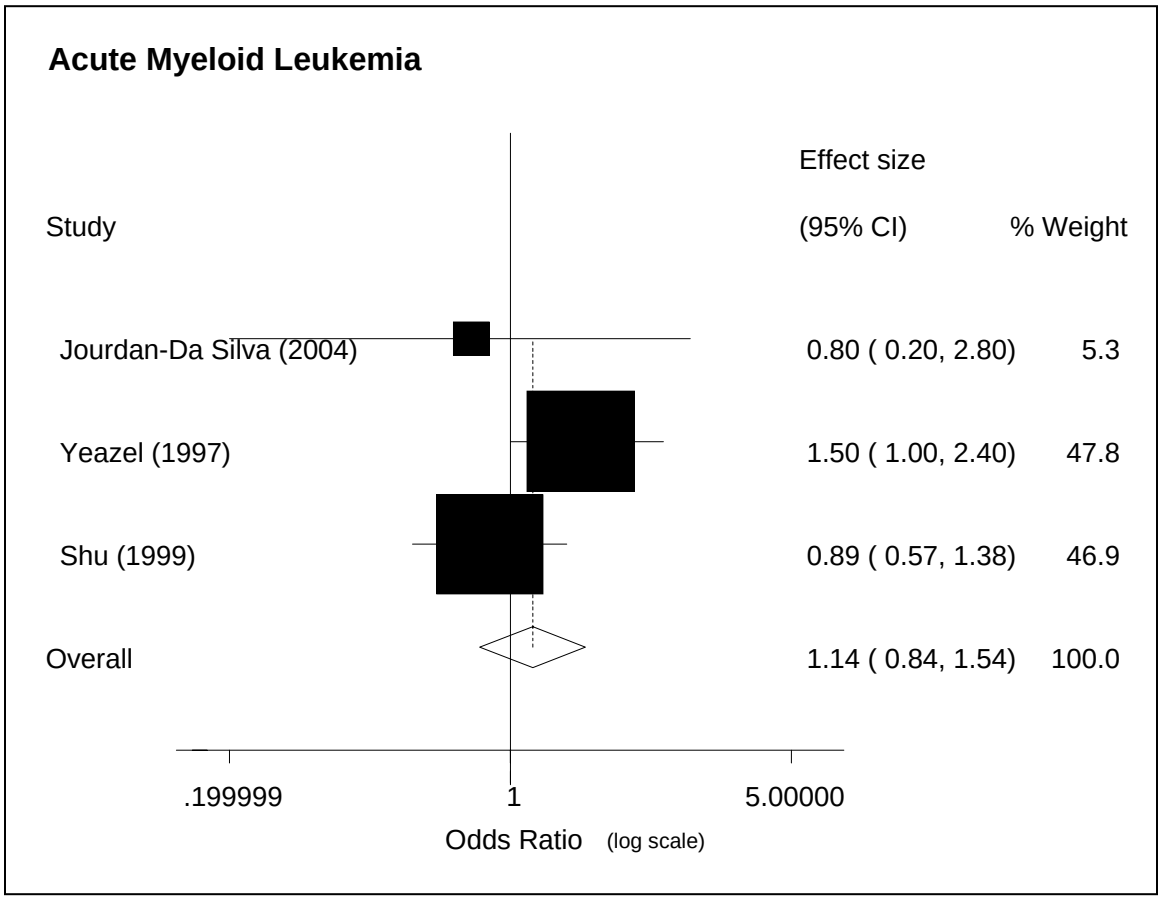
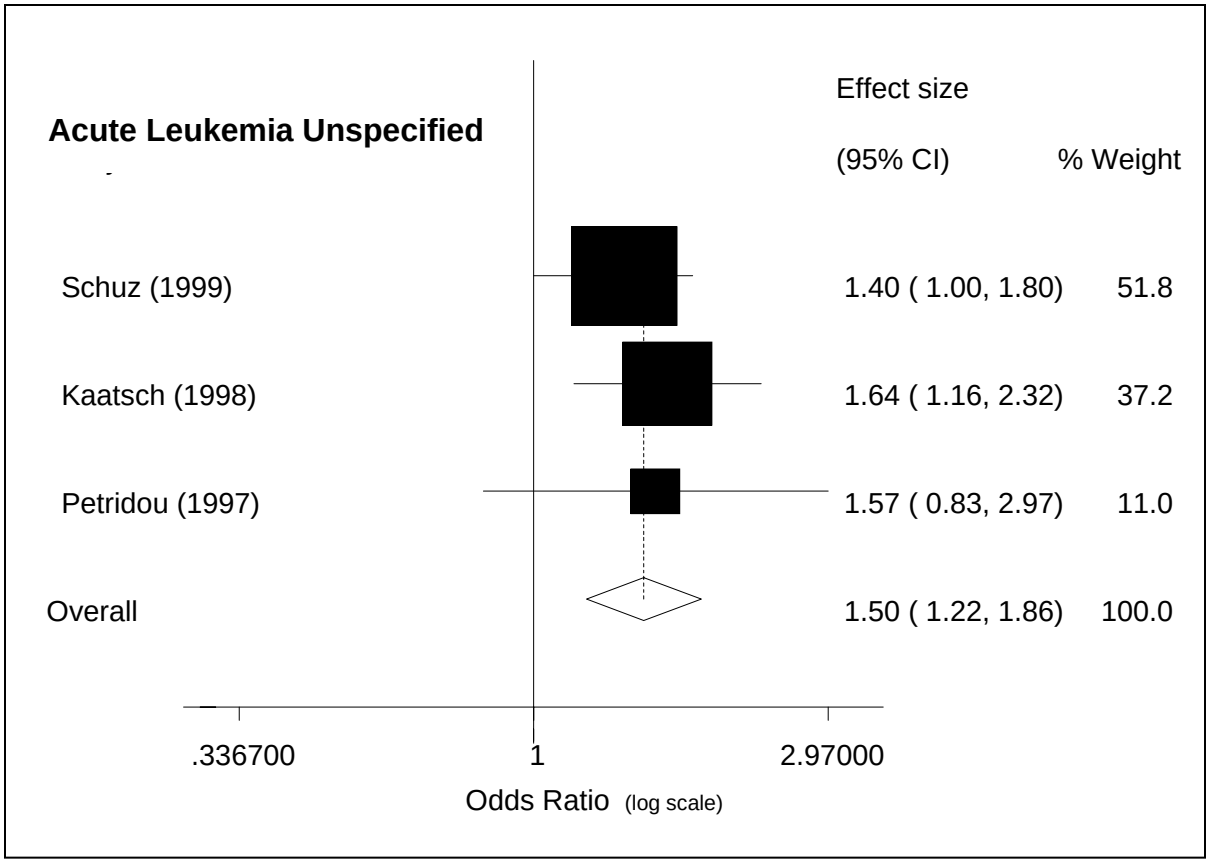


Figure 10. Odds ratios with corresponding 95% confidence intervals for AML in children with high birth weight (≥4000 g).*



* For each study, the size of the boxes is proportional in area to the weight that the study has in calculating the summary odds ratio. Fixed effects summary odds ratios are displayed since there was no evidence of statistical heterogeneity across studies.

Figure 11. Odds ratios with corresponding 95% confidence intervals for acute leukemia unspecified in children with high birth weight (≥4000 g)*



* For each study, the size of the boxes is proportional in area to the weight that the study has in calculating the summary odds ratio. Fixed effects summary odds ratios are displayed since there was no evidence of statistical heterogeneity across studies.

3.4 Subgroup Analysis

Since there were few studies of AML and of acute leukemia unspecified, subgroup analysis was limited to studies of ALL. Table 7 shows overall odds ratios of ALL associated with high birth weight by various study characteristics. Overall odds ratios were calculated using a fixed effects model. These stratified analyses yielded relatively similar overall odds ratios. For example, after one study that was available only as a dissertation[116] was excluded, the overall odds ratio increased slightly to 1.26. When the analysis was confined to those studies that reported $\geq$ 70% response rates among cases and controls, the overall odds ratio was reduced only slightly, to 1.23. When the analysis was confined to the four studies that used a birth registry as the source of birth weight data, the overall odds ratio was reduced to 1.17. Given that ALL is the predominant form of leukemia in children, an overall odds ratio was calculated combining studies of acute leukemia unspecified (3 studies) with the nine studies of ALL. This addition increased the overall odds ratio to 1.29. Finally, when analysis was confined to those studies identified using Medline, the overall odds ratio was reduced only slightly to 1.23. As expected, less precision resulted as shown by a wider 95% confidence interval (1.10-1.39) and fewer studies in the analysis meant a loss of power.

Table 7. Overall Odds Ratio of ALL and High Birth Weight (>4000 g) among Children in Studies that used Different Criteria

Studies Included in Analysis	No. Studies	Overall Odds Ratio (95% CI)	P value for Heterogeneity
All studies of ALL	9	1.24 (1.12-1.37)	0.26
Studies that addressed confounding[@]	9	1.24 (1.12-1.37)	0.26
Peer-reviewed studies*	8	1.26 (1.13-1.40)	0.24
Studies that reported ≥70% response rate among cases and controls	5	1.23 (1.09-1.39)	0.17
Studies that reported < 70% response rate among cases and controls	4	1.27 (1.05-1.53)	0.31
Studies that used a registry as source of birth weight data	4	1.17 (0.99-1.38)	0.13
Studies that used interview as source of birth weight data	5	1.35 (1.16-1.59)	0.47
Studies of ALL plus studies of acute leukemia unspecified	12	1.29 (1.17-1.41)	0.28
Studies identified with Medline	6	1.23 (1.10-1.39)	0.19

[@] Through matching or adjustment or both
* The dissertation by Rosenbaum PF (116) was excluded

Table 8 shows stratified analyses according to different reference birth weights. The overall odds ratio varied somewhat depending on the reference birth weight used. Among studies using a reference birth weight of 2500-4000 g and studies using a reference birth weight of 3000-3500 g, high birth weight does not appear to be significantly associated with ALL. In contrast, studies using reference birth weights of ≤ 3000 g and ≤ 4000 g show a statistically significant association between high birth weight and ALL. However, the number of studies in each stratum is very small and therefore, these results must be interpreted with caution. The ≤ 3000 g and ≤ 4000g reference birth weight categories include

low birth weight babies (< 2500 g). As such the overall odds ratios derived from these categories could be explained by inadequate adjustment for confounding variables such as smoking and gestational age. In fact, the one study[22] that used ≤ 3000 g for its reference birth weight neither adjusted for nor matched on smoking or gestational age. Of the two studies[14,27] that used ≤ 4000 g as its reference birth weight, only one adjusted for gestational age and neither study adjusted for nor matched on smoking.

Whether the magnitude of effect of ALL varies by age of diagnosis was unable to be tested because only two studies included in the present meta-analysis presented data stratified by age and not in identical age strata.[8,11]

Table 8. Overall Odds Ratio of ALL and High Birth Weight (>4000 g) among Children in Studies that used Different Reference Birth Weights

Reference Birth Weight of Studies Included in Analysis*	No. Studies	Overall Odds Ratio (95% CI)	P value for Heterogeneity
All studies of ALL	9	1.24 (1.12-1.37)	0.26
2500-4000 g	4	1.13 (0.96-1.32)	0.14
3000-3500 g	2	1.21 (0.96-1.52)	0.55
≤ 3000 g	1	1.40 (1.10-1.80)	0
≤ 4000 g	2	1.37 (1.10-1.69)	0.28

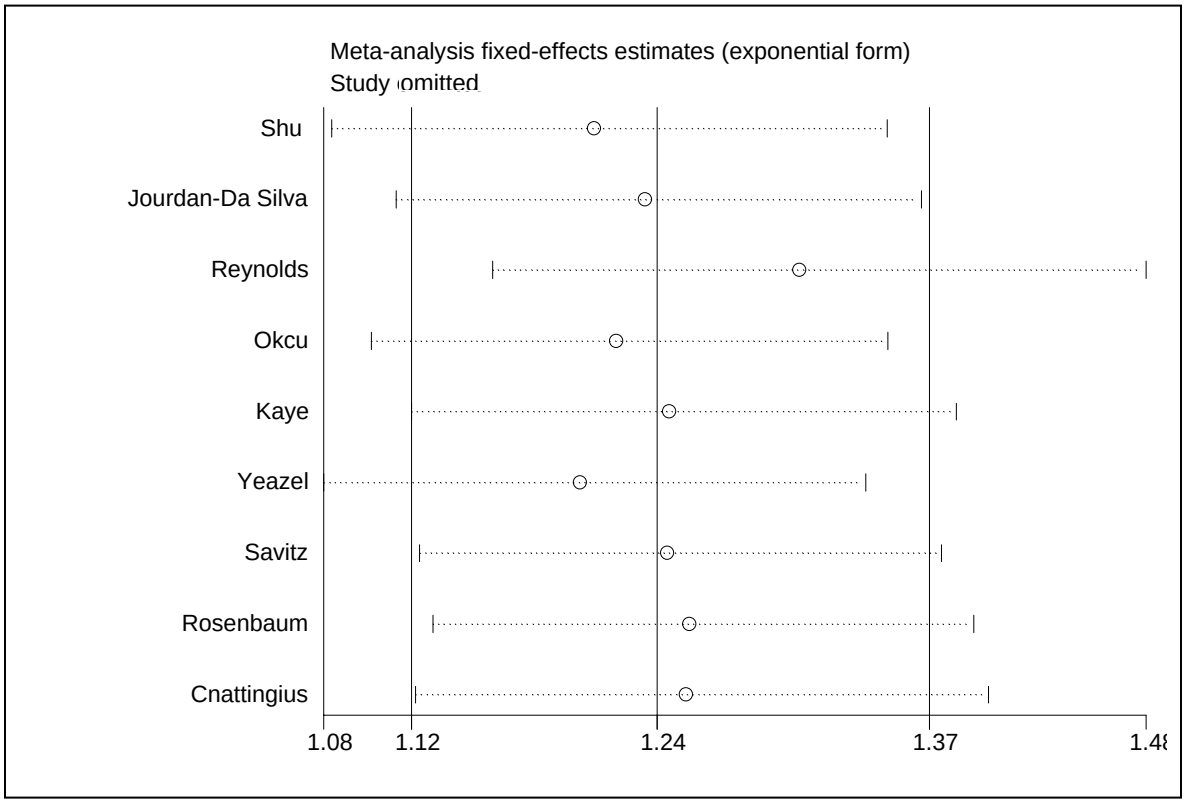
***** Rounded to the nearest gram

3.5 Sensitivity Analysis

Figure 12 investigates the influence of a single study on the overall meta-analysis estimate based on the nine studies of ALL. The overall odds ratio is

computed omitting one study in each instance. As seen in Figure 12, the exclusion of any individual study did not produce statistically significant changes to the overall odds ratio. No individual study had a dominant influence. However, exclusion of the study by Reynolds et al.[33] shifted the overall odds ratio the most. This study had the largest sample size (cases=1407; controls=2811; total=4218) and reported an odds ratio of 1.09 that included the null value (95% CI: 0.90, 1.31) so that its exclusion led to a shift of the overall odds ratio to the right.

Figure 12. Influence of Excluding An Individual Study on the Overall Odds Ratio of ALL and High Birth Weight (Based on Nine Studies on ALL)



3.6 Secondary Meta-Analysis

The analyses in the above sections 3.2 thru 3.5 were limited to studies using a high birth weight cutoff of > 4000 g (per inclusion criteria). This section 3.6 reports results of a secondary meta-analysis that included studies with high birth weight cutoffs other than > 4000 g. Five studies of ALL, two of AML, and one of acute leukemia unspecified were added to the studies in the main meta-analysis. Characteristics of these additional studies are depicted in Tables 8A, 8B, 8C, and 8D.

Table 8A. Characteristics of Studies that had a High Birth Weight Cutoff other than > 4000 g and were Included in the Secondary Meta-Analysis

Author (reference no.)	Publication year	Database source*	Case recruitment period	Country	Study type	Cases (no.)	Controls (no.)	Age range (yrs)
Acute lymphoblastic leukemia								
Westergaard T (26)	1997	M	1968-1992	Denmark	Cohort	399	Cohort	< 15
Murray L (21)	2002	M	1975-1997	N. Ireland	Cohort	146	345,473	< 16
McKinney PA (100)	1999	M	1991-1994	Scotland	Case-control	124	236	< 15
Shu XO (17)	1988	M	1974-1986	China	Case-control	172	344	< 15
Roman E (35)	1997	M	1962-1992	U.K.	Case-control	113	226	< 30
Acute myeloid leukemia								
Westergaard T (26)	1997	M	1968-1992	Denmark	Cohort	65	Cohort	< 15
Roman E (35)	1997	M	1962-1992	U.K.	Case-control	15	30	< 30
Acute leukemia unspecified								
Shu XO (101)	1994	M	1986-1991	China	Case-control	166	166	< 15

* M=Medline

Table 8B. Characteristics of Studies that had a High Birth Weight Cutoff other than > 4000 g and were Included in the Secondary Meta-Analysis (continued)

Author (reference no.)	Outcome	Source of Cases	Source of Controls	Birth Weight Source	Case Response Rate	Control Response Rate	Matching Factors*	Adjusting Factors*
Acute lymphoblastic leukemia								
Westergaard T (26)	ALL, AML incidence	Cancer registry	Population cohort	Registry	58%	--	NR	BD, BO, CP, MA, S
Murray L (21)	ALL incidence	Cancer registry	Population cohort	Registry	78%	80%	NR	DS, S
McKinney PA (100)	ALL incidence	Cancer registry	Population	Registry and interview	96%	93%	BD, G, S	NR
Shu XO (17)	ALL incidence	Cancer registry	Community	Interview	94%	98%	AD, S	BO, BP
Roman E (35)	ALL, AML incidence	Cancer registry	Population	Registry	90%	92%	BD, BP, S	NR
Acute myeloid leukemia								
Westergaard T (26)	ALL, AML incidence	Cancer registry	Population cohort	Registry	58%	--	NR	BD, BO, CP, MA, S
Roman E (35)	ALL, AML incidence	Cancer registry	Population	Registry	90%	92%	BD, BP, S	NR
Acute leukemia unspecified								
Shu XO (101)	Acute leukemia incidence	Cancer registry	Population	Interview	83%	100%	AD, G, S	NR

* AD, age at diagnosis; BO, birth order; BD, birth date; BP, birthplace; CP, calendar period; DS, Down's Syndrome; G, geographic location at diagnosis; GA, gestational age; MA, maternal age; NR, not relevant; P, Parity; R, race; S, sex; SES, socioeconomic status; SM, smoking; T, Tobacco use

Table 8C. Characteristics of Studies that had a High Birth Weight Cutoff other than > 4000 g and were Included in the Secondary Meta-Analysis (continued)

Author (reference no.)	Ethnicity Data	High Birth Weight (HBW)	% HBW Cases	% HBW Controls
Acute lymphoblastic leukemia				
Westergaard T (26)	Not reported	≥ 4010	17.0	11.3
Murray L (21)	Not reported	≥ 3500	48.9	41.6
McKinney PA (100)	White 4.8% (cases), 4.2% (controls) Non-white 95.2% (cases), 95.8% (controls)	≥ 3500	42.3	40.3
Shu XO (17)	Not reported	≥ 3500	31.4	24.3
Roman E (35)	Not reported	> 3500	36.3	37.6
Acute myeloid leukemia				
Westergaard T (26)	Not reported	≥ 4010	20.0	11.3
Roman E (35)	Not reported	> 3500	60	20
Acute leukemia unspecified				
Shu XO (101)	Not reported	> 3700	19	14

Table 8D. Characteristics of Studies that had a High Birth Weight Cutoff other than > 4000 g and were Included in the Secondary Meta-Analysis (continued)

Author (reference no.)	Referent Birth Weight (RBW)	% RBW Cases	% RBW Controls	Odds Ratio (95% CI)	Miscellaneous
Acute lymphoblastic leukemia					
Westergaard T (26)	3010-3509	33.1	36.6	1.67 (1.25-2.24)*	
Murray L (21)	< 3500	51.1	58.4	1.66 (1.18-2.33)**	
McKinney PA (100)	2500-3499	52.0	55.5	1.17 (0.74-1.85)	
Shu XO (17)	< 3000	33.1	26.4	1.50 (0.90-2.30)	
Roman E (35)	2500-3500	58.4	58.4	0.90 (0.60-1.50)	
Acute myeloid leukemia					
Westergaard T (26)	3010-3509	35.4	36.6	1.66 (0.83-3.31)*	
Roman E (35)	2500-3500	40	76.7	6.20 (1.30-29.80)	Mean birth weight (standard error) 3615 (107) (cases); 3215 (84) (controls)
Acute leukemia unspecified					
Shu XO (101)	<3000	19	31	2.21 (0.90-5.41)	

* Rate ratio ** Risk ratio

Table 9 shows the overall odds ratio of the secondary meta-analysis by various criteria. For ALL, varying the cutoff for high birth weight did not substantially change the strength of the association between high birth weight and ALL, nor did subtracting the Chinese study.[17] When analysis was confined to studies with a predominantly non-Hispanic White population, the overall odds ratio increased to 1.34 (95% CI: 1.21, 1.49). As shown in Tables 6C and 8C, information on the ethnic makeup of the study population was often not reported. An expert (Dr. Michele Forman) who was familiar with and knowledgeable about these studies, provided a recommendation for which studies to include in the analysis of studies of non-Hispanic white population. Figure 13 depicts the study-specific odds ratios and the overall odds ratio for the 14 studies of ALL with

varying cutoffs for high birth weight. As shown in Figure 13, two studies[35, 115] report an odds ratio less than 1.0. One of these studies (by Savitz) is previously discussed in section 3.3. The other study by Romans[35] reports an odds ratio of 0.90 (95% CI: 0.60, 1.50). This study spans 30 years from 1962-1992 in its case recruitment period. Changes in the diagnosis of ALL potentially could have occurred during this time. In addition, this study defines a high birth weight cutoff of > 3500 grams and includes an older study population with cases aged < 30 years.

For AML, changing the cutoff for high birth weight resulted in an overall odds ratio that varied from 1.14 (95% CI: 0.84, 1.54) to 1.36 (95%CI: 0.87, 2.12). In contrast, for acute leukemia unspecified, the overall odds ratio did not substantially change when studies with varying cutoffs for high birth weight were included.

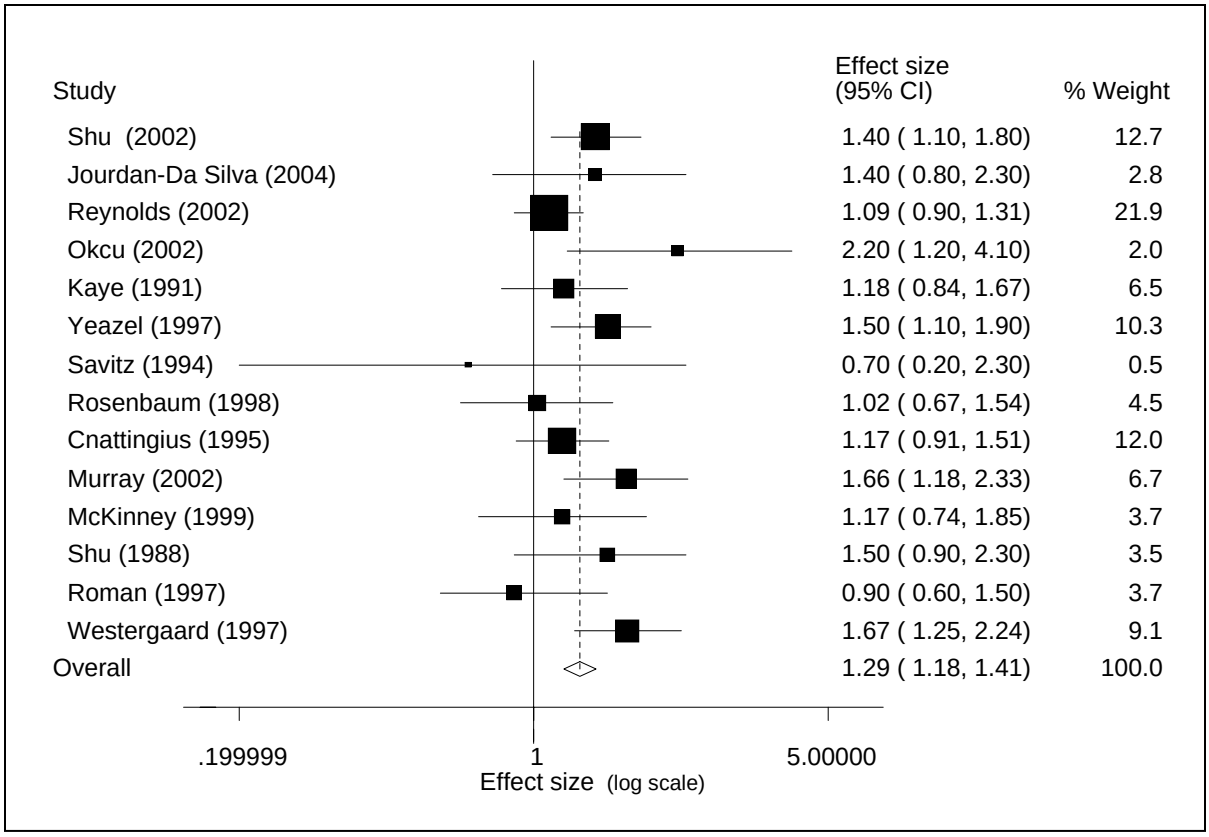
Table 9. Overall Odds Ratio of Secondary Meta-Analysis by Different Criteria

Studies Included in Analysis	No. Studies	Overall Odds Ratio (95% CI)	P value for Heterogeneity
Acute Lymphoblastic Leukemia			
Studies with HBW cutoff >4000 g	9	1.24 (1.12-1.37)	0.26
Studies with HBW cutoff >4000 g or >3500 g	13	1.26 (1.15-1.38)	0.22
Studies with HBW cutoff >4000 g or >3500 g or >4010 g	14	1.29 (1.18-1.41)	0.13
Studies with HBW cutoff >4000 g or >3500 g minus Chinese Study[17]	12	1.25 (1.14-1.37)	0.19
Studies with HBW cutoff >4000 g or >3500 g or >4010 g minus Chinese Study[17]	13	1.28 (1.17-1.40)	0.11
Studies of Non-Hispanic White Population*	9	1.34 (1.21-1.49)	0.22
Acute Myeloid Leukemia			
Studies with HBW cutoff >4000 g	3	1.14 (0.84-1.54)	0.22
Studies with HBW cutoff >4000 g or >3500 g	4	1.31 (0.74-2.32)**	0.06
Studies with HBW cutoff >4000 g or >3500 g or >4010 g	5	1.36 (0.87-2.12)**	0.09
Acute Leukemia Unspecified			
Studies with HBW cutoff >4000 g	3	1.50 (1.22-1.86)	0.78
Studies with HBW cutoff >4000 g or > 3700 g	4	1.54 (1.25-1.89)	0.76

* Included the studies by Shu,[22] Jourdan-Da Silva,[114] Kaye,[14] Cnattingius,[24] Rosenbaum,[116] Yeazel,[27] Westergaard,[26] Murray,[21] Roman[35]

** Random effects model used

Figure 13. Odds ratios with corresponding 95% confidence intervals for ALL in children with high birth weight (of varying cutoffs)*



* For each study, the size of the boxes is proportional in area to the weight that the study has in calculating the summary odds ratio. Fixed effects summary odds ratios are displayed since there was no evidence of statistical heterogeneity across studies.

3.7 Publication bias

No evidence of publication bias was indicated through a variety of visual and statistical tests. Figure 14 shows the Begg funnel plot depicting an absence of publication bias. Funnel plots are simple scatter plots of the effect size estimated from individual studies against some measure of study size. In the Begg funnel plot, effect measure is plotted against standard error, a measure that reflects the precision of the effect size estimate. The name “funnel plot” derives from the fact that the precision in the estimation of the underlying effect will increase as the sample size of component studies increases.[37] The effect estimates from small, less precise studies will therefore scatter more widely, with the spread narrowing among larger, more precise studies. In the absence of publication bias, the data from all studies should take the shape of a funnel with the tip of the funnel centered on the true effect size. If there is bias against the publication of small studies with null results, the pyramidal corners of the funnel will be distorted or missing. The Begg adjusted rank correlation test applied to the nine studies of ALL (where high birth weight > 4000 g) and to the 14 studies of ALL (with varying cutoffs for high birth weight) did not indicate the presence of publication bias ($p=0.53$ and $p=0.78$, respectively).The Begg test is a direct statistical analogue of the visual funnel graph. The Begg procedure tests for publication bias by determining if there is a significant correlation between the effect estimates and their variances.[85]

Figure 14. Begg's Funnel Plot of Nine Case-Control Studies of ALL and High Birth Weight (> 4000 g)

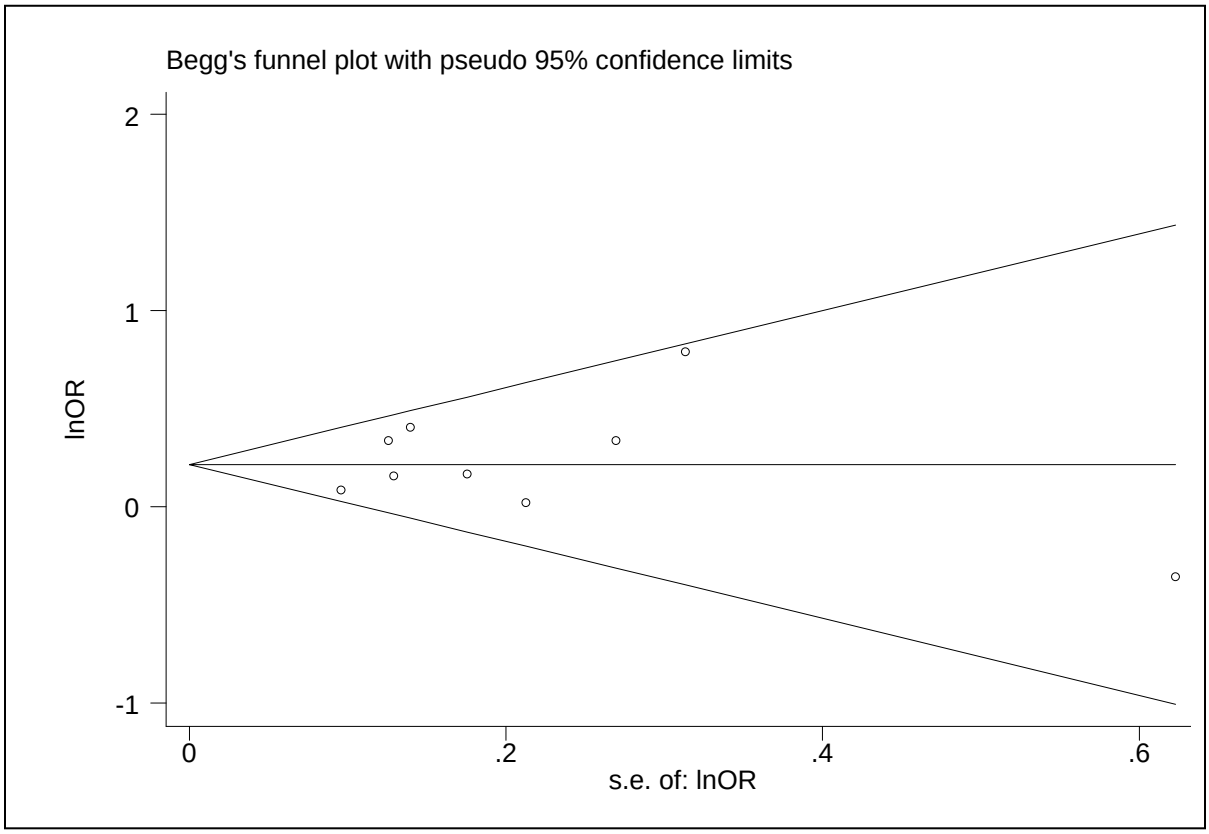
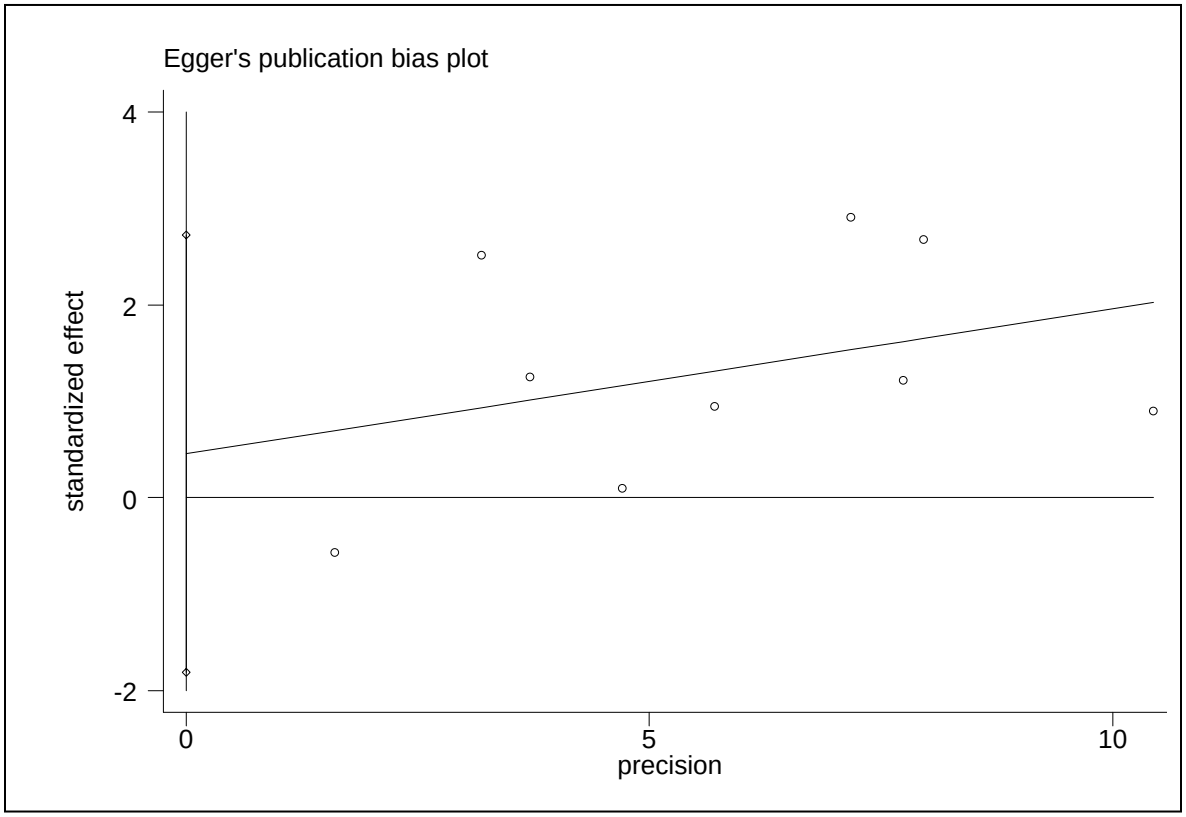


Figure 15 shows the Egger regression asymmetry plot that also indicates the absence of publication bias (p=0.65). The Egger test detects funnel plot asymmetry by determining whether the intercept deviates significantly from zero in a regression of the standardized effect estimates against their precision.[86]

Lastly, the sensitivity of results to possible unpublished studies was assessed using two methods, a “file drawer” test and the Duval-Tweedy “trim and fill” method. The Duval-Tweedy nonparametric test indicated that no trimming was performed and the data left unchanged. This technique estimates the number and outcomes of missing studies, and adjusts the meta-analysis to incorporate the theoretical missing studies.[83]

The file drawer test estimates the number of unpublished null studies (OR=1.0) that would need to exist to negate the results of the published studies that were included in the meta-analysis.[87] This test indicated that three unpublished null studies would be required to negate the results of the main meta-analysis regarding ALL and high birth weight (> 4000 g) and nine unpublished null studies would be required to negate the results of the secondary meta-analysis regarding ALL and high birth weight (with varying cutoffs for high birth weight).

Figure 15. Egger's Publication Bias Plot Applied to Nine Case-Control Studies on ALL.



4. DISCUSSION

4.1. Summary of Key Findings

The major objective of this study was to determine whether high birth weight is associated with ALL and AML among children and to quantify the strength of the relationships. To this end, we conducted a meta-analysis of nine case-control studies (published between 1991 and 2004) encompassing over 6,200 children with ALL and over 12,000 controls. We found that children weighing 4,000 g or more at birth had 24% (OR: 1.24; 95% CI: 1.12, 1.37) higher odds of developing ALL than children weighing less (without consideration to reference weight). Once we found that high birth weight was positively associated with ALL, through subgroup analysis we demonstrated consistency of findings across studies included in our meta-analysis. Regardless of peer-review status, response rates among cases and controls, or choice of threshold for high birth weight (4,000 g, 3,500 g, or 4,010 g), studies consistently demonstrated a similar overall odds ratio ranging from 1.23 to 1.29 (Table 7 and 9). Lack of statistical heterogeneity among studies was also documented.

Our data supports the growing evidence for the link between high birth weight and childhood ALL and confirms the results of another meta-analysis involving children with leukemia.[94] This other meta-analysis concluded that birth weight of 4,000 g or more was associated with an increased risk of ALL (OR: 1.26; 95% CI: 1.17, 1.37; N= 13 studies) compared with birth weights less than 4,000 g.[94] (A more complete comparison of the two meta-analyses is discussed in section 4.7)

Whether a similar positive association with high birth weight applies to AML is less clear from our results. Based on a meta-analysis of only three case-control studies (published between 1997 and 2004) involving over 700 children with AML and over 1,900 controls, high birth weight ($\geq$ 4,000 g) appeared to increase the odds of developing AML by 14% (OR: 1.14; 95% CI: 0.84, 1.54). This association did not reach statistical significance and should be interpreted with caution as the number of studies was small.

A second objective of our study was to explore the reasons for inconsistent findings among previous studies. While evidence for the link between high birth weight and ALL is mounting, some studies have not demonstrated this association. It is uncertain whether the different findings across studies were due to differences in study population or design. Our data analysis identified possible reasons for inconsistent findings among previous studies that examined high birth weight as a risk factor for ALL. Possible explanations include: use of different reference birth weights, different data source for birth weight (i.e., birth certificate vs. interview), and different ethnic makeup of the study population. First, we found that choice of reference birth weight affected the strength of the association between high birth weight and ALL. Compared to an overall odds ratio of 1.24 (95% CI: 1.12, 1.37) when the reference was all newborns weighing less than 4,000 g (low birth weight [LBW] + normal birth weight [NBW]), the odds ratio changed to 1.13 (95% CI: 0.96, 1.32) when newborns weighing from 2,500-4,000 g (NBW) were the referent category. The odds ratio changed to 1.21 (95% CI: 0.96, 1.52) when only newborns weighing 3,000-3,500 g were considered; to

1.40 (95% CI: 1.10, 1.80) when only < 3,000 g was the referent category; and finally the odds ratio changed to 1.37 (95% CI: 1.10, 1.69) when only < 4,000 g was the referent category (Table 8).

Second, another explanation to account for heterogeneity across studies involves the source of birth weight data – through birth certificates or maternal interview. Studies based on birth certificate data showed an overall odds ratio of 1.17 (95% CI: 0.99, 1.38; N=four studies) whereas those that relied on maternal interview data had an overall odds ratio of 1.35 (95% CI: 1.16, 1.59; N=five studies) (Table 7). While these point estimates fall within each other's confidence interval, this is the largest change in magnitude of odds ratio among variables considered in our subgroup analysis. Further discussion of birth certificate data versus maternal recall is found in section 4.6.

Third, in addition to differences in reference birth weight and data source for birth weight, another explanation for variability includes differences in the ethnicity of the study population. In other words, effect modification by ethnicity could account for heterogeneity of results. Several studies in our meta-analysis did not report or consider ethnic differences in study populations. Lack of ethnicity information is problematic as racial and ethnic differences occur for lymphoid leukemias. Whites have the highest rates in the United States, followed by those for blacks, Hispanics, and Chinese; rates are lowest and similar for Filipinos, Hawaiians, and Japanese.[3,6] Accordingly, we found that when analysis was confined to studies with a predominantly non-Hispanic white population, the overall odds ratio increased from 1.24 (1.12-1.37) to 1.34 (95% CI: 1.21, 1.49)

(Table 9). An expert (Dr. Michele Forman) familiar with and knowledgeable about these studies provided a recommendation regarding which studies to include in the subgroup analysis of studies of non-Hispanic white population as several studies did not publish ethnicity data. Inclusion of Hispanics in these studies potentially would have resulted in an attenuation of the overall odds ratio.

4.2. Biologic Mechanism

Like other cancers, childhood leukemia is thought to occur as a consequence of successively acquired specific genetic aberrations. Studies have shown that cells with certain chromosomal translocations specific to leukemic cells, such as t(12;21), t(4;11), or t(8;21), are often already present at birth in children who later develop leukemia, indicating that the development of childhood leukemia can start in utero.[119,120] Ultimately, this process leads to the uncontrolled proliferation and accumulation of immature, nonfunctional lymphoblasts in the bone marrow and, to a lesser extent, in the blood.[1] How the association between birth weight and leukemia risk might fit into this process remains unclear.

Various biologic mechanisms have been suggested to explain the association between birth weight and the risk of acute leukemia in children. Specifically, high levels of insulin-like growth factor 1 is associated with high birth weight and may play a role in the development of childhood leukemia by exerting a proliferative stress (i.e., an increase in the number of cell divisions) on existing pre-leukemic cells.[73] Proliferation of existing pre-leukemic cells could increase the chance of a spontaneous mutation, which can lead to cancer.[73] Another

related hypothesis suggests that, because there is an association between birth weight and bone marrow volume (number of bone marrow cells), children with a higher birth weight have more cells at risk of malignant transformation and are thus at a greater risk of leukemia.[121] High birth weight could reflect an increased probability of mutation since a larger child would have a greater number of cell divisions. A third hypothesis is that in utero exposure to high endogenous estrogen levels, one of the predictors of birth weight, is involved in the etiology of childhood ALL.[74] Another theory – one of reverse causality -- suggests that pre-leukemic cells stimulate growth and cause high birth weight in children with leukemia.[122]

Birth weight may merely act as a marker for one or more processes that predispose to leukemia rather than reflect a causal relationship. If so, modifying birth weight might not change the risk of acute leukemia in children. For example, fetal growth factors, such as insulin-like growth factor 1 could stimulate proliferation of both normal and malignant cells that could explain why high birth weight babies have a higher risk of leukemia. In addition, it has been previously suggested that children with a high birth weight may be more likely to be exposed to diagnostic radiation in utero or in the neonatal period and that this radiation exposure might explain some of the excess risk associated with high birth weight.[29]

The development of childhood leukemia may be a multifaceted process that involves not only prenatal risk factors but also postnatal ones. That more children (100-fold more) may be born with leukemia-associated genetic aberrations than

will ultimately develop ALL, suggests that postnatal risk factors are critical to the development of ALL.[123] In addition, there may be discrete windows of vulnerability to exogenous exposures. One example is the statistical association between prenatal exposure to diagnostic radiographs, particularly during the last trimester of pregnancy, and subsequent increase in childhood acute leukemia risk (about 1.5 times).[124]

There is little current insight into the natural history of acute leukemia in children and the likely timing of key exposures and mutational events. A small but significant proportion (up to 5%) of acute leukemias (both myeloid and lymphoblastic) are associated with genetic and congenital disorders.[6] Children with Down's syndrome account for approximately 2 per cent of all cases of childhood ALL diagnosed and are estimated to have as high as a 20-fold increased risk for development of acute leukemia.[125] Other groups of children who have been found to have an elevated risk for leukemia include those with neurofibromatosis type 1, ataxia telangiectasia, Fanconi syndrome, and Bloom syndrome.[3,5,6,10] For example, one study found that the frequency of neurofibromatosis type 1 in Japanese children with leukemia (0.21%) was significantly increased over that estimated in comparable Japanese children (0.03%).[126] Moreover, as many as one third of patients with ataxia telangiectasia, a rare autosomal recessive disorder, develop cancer, the majority of which are leukemias and lymphomas.[127,128]

The best-substantiated causal mechanism for acute leukemia is via ionizing radiation which damages cells by disrupting chemical bonds and causing

chromosomal abnormalities. High doses of ionizing radiation from environmental and therapeutic sources have been associated with childhood acute leukemias, as have lower doses of ionizing radiation, such as that from diagnostic radiography during pregnancy. [6] Much of the current understanding of the carcinogenic effects of ionizing radiation exposure arises largely from studies of the Japanese survivors of the atomic bombings of Hiroshima and Nagasaki in 1945. [129] Although the principal concern in the immediate aftermath of the bombings was the potential offspring of these survivors, it is the excess risk of cancer among the survivors themselves that has proved to be the main long-term health effect resulting from radiation exposure during the bombings.[130] Japanese children and adults exposed to high radiation levels experienced an increased risk (20- to 25-fold increase) of leukemia that peaked about five years after the atomic bomb blasts. [1] Children born to women pregnant at the time of the blasts in Japan did not develop an elevated occurrence of leukemia. [131] (Some researchers have attributed this finding to limited statistical power and the fact that mortality from childhood leukemia was unrecorded from 1946 to 1949 because the Japanese survivors were systematically monitored only from 1950.[124]) However, an excess of acute leukemia has been observed among children born and residing in proximity to Sellafield nuclear reprocessing plant in Great Britain despite very low measured radiation levels.[132] Some studies on paternal occupational exposure have shown leukemia increases among children whose fathers were employed in the nuclear industry while others have demonstrated no increases. For example, recorded external dose of whole body

ionizing radiation to fathers during their time at Sellafield nuclear reprocessing plant was associated with development of leukemia in their offspring.[133] Children whose fathers had a lifetime cumulative dose of 100 mSv or more before conception were estimated to be 8.4 (95% CI: 1.4, 52.0) times more likely to develop leukemia. [133] Other studies conducted in the vicinity of other nuclear establishments where workers were, on average, exposed to much lower doses, were unable to confirm these findings.[134,135] Finally, high levels of radioactive iodine and caesium were released in the Chernobyl reactor failure, but to date no increase in acute leukemia among children or adults has been recorded in the regions most exposed. [11]

High doses of ionizing radiation, not only from environmental sources but also from radiotherapy treatments, have been linked with elevated childhood acute leukemia risk. Children who received therapeutic irradiation for ankylosing spondylitis, a painful condition of the spine, have almost a tenfold increase in the number of leukemias.[1] An excess of leukemias have also been reported in children treated with therapeutic radiation for fungal infection of the scalp or for enlarged thymuses.[132]

4.3. Determinants of Birth Weight

The finding that birth weight is positively associated with childhood ALL prompts the consideration of the determinants of birth weight. Birth weight is determined by intergenerational factors, ethnicity, and a range of other exposures. [48,136] Hennessy and Alberman showed that birth weight for gestational age, representing fetal growth rate, is explained best by factors relating to the

parent's own growth. [48] The researchers found that both maternal and paternal birth weight for gestation were the most important predictors of fetal growth. [48] Klebanoff and colleagues demonstrated a strong association between maternal birth weight and the delivery of a baby weighing more than 4000 g.[49] Compared to infants of mothers who themselves weighed $\geq$ 8 pounds, infants of mothers who weighed 6 to 7.9 pounds were at 36% the risk ($p < 0.0001$) and infants of mothers who weighed 4 to 5.9 pounds were at 14% the risk ($p=0.0002$) of having an infant > 4000 g). [49] Not only is maternal birth weight important, but also paternal birth size is as well.[137] Klebanoff and colleagues showed that independently of maternal birth size, paternal birth size influences the birth weight of his children. [137] These authors report that cumulatively, paternal birth weight, adult height, and adult weight explained approximately 3% of the variance in infant birth weight compared with 9% for the corresponding maternal factors. [137]

Other risk factors for high birth weight have been noted. Mothers of babies weighing more than 4,000 g are older (26.9 versus 25.7 years, $p=0.03$), heavier (61 versus 57.6 kg, $p=0.002$), taller (165.9 versus 163.2 cm, $p<0.0001$), and gained more weight (13.2 versus 11.0 kg, $p=0.0008$) than mothers of other infants.[49] Moreover, the pattern of maternal weight gain during pregnancy is as important as the total amount. [45,56] Studies have pointed to the importance of second trimester rate of gain in determining birth weight. [45,56] For example, one study showed that low weight gain in the first and second or in the second and third trimesters was associated with significant decreases in birth weight whereas

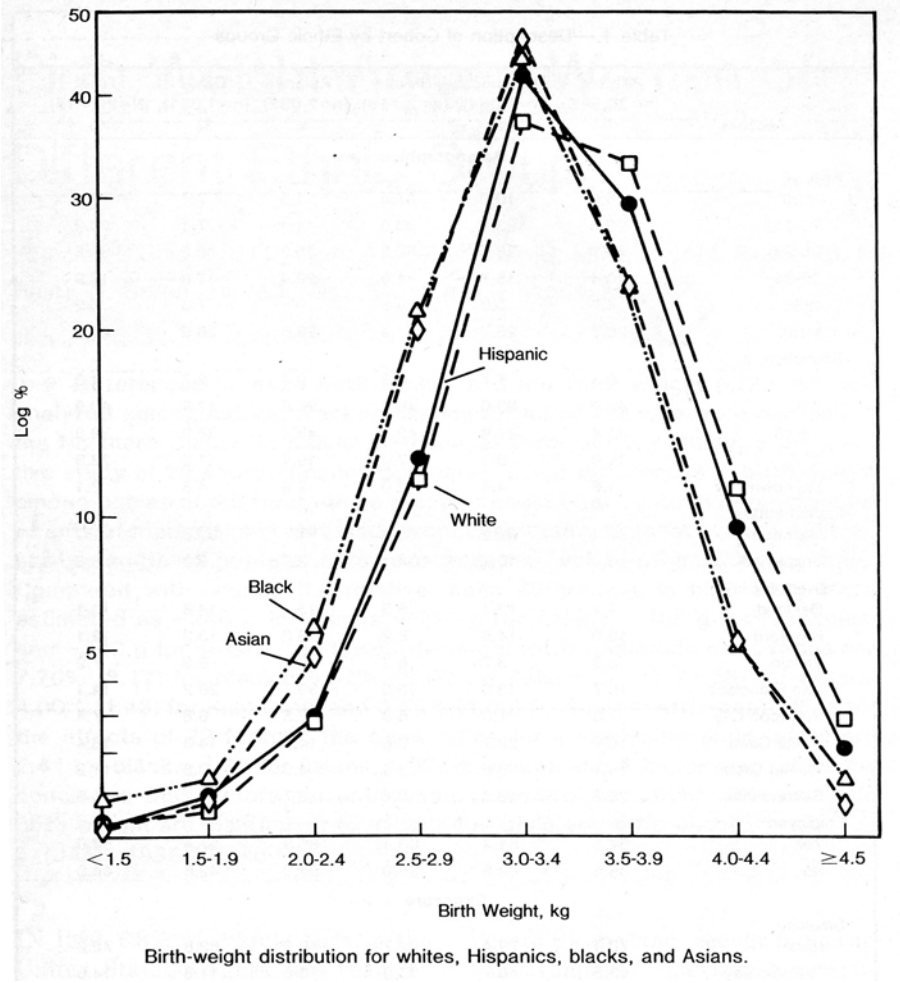
no important change in birth weight was seen for low gain in the first and third trimesters.[56]

In addition, delivering a high birth weight baby (> 4000 g) is more common among higher-order multi-gravid women (4.5% for gravida 1, 5.9% for gravida 2 or 3, 10.2% for gravida 4+; p=0.008) and less common among smokers (8.7% among non-smokers, 3.8% for ≤ ½ pack per day, 3.0% for > ½ pack per day; p=0.0005).[49] Offspring of mothers with gestational diabetes mellitus have higher birth weights since maternal hyperglycemia leads to excess fetal insulin, itself a growth hormone for the fetus. [49] As expected, male infants were more likely than female infants to weigh more than 4000 g (8.3% versus 4.1%; p=0.0015).[49]

Ethnicity also affects birth weight. Figure 16 plots the birth weight distribution by ethnic group among Asians, Blacks, Hispanics, and Whites enrolled in a Northern California prospective cohort study of over 29,000 women. [136] The curves for Whites and Hispanics are shifted to the right, denoting the heavier overall birth weight distribution for these groups. The mean birth weight for Whites, Hispanics, Asians, and Blacks was 3.48 kg, 3.42 kg, 3.26 kg, and 3.23 kg, respectively. Adjusting for gestational age, the authors found that on average, Hispanics, Asians, and Blacks had babies that were 72 g, 167 g, and 183 g lighter than did Whites, respectively. [136] Not only does ethnicity affect birth weight, but also racial and ethnic differences occur for lymphoid leukemias. As noted earlier, Whites have the highest rates in the United States, followed by those for blacks, Hispanics, and Chinese; rates are lowest and similar for Filipinos, Hawaiians, and Japanese.[3,6] Accordingly, we found that when our

meta-analysis was confined to studies with a predominantly non-Hispanic white population, the overall odds ratio increased from 1.24 (1.12-1.37) to 1.34 (95% CI: 1.21, 1.49) (Table 9).

Figure 16. Birth Weight Distribution for Whites, Hispanics, Blacks, and Asians



Birth-weight distribution for whites, Hispanics, blacks, and Asians.

4.4. Strengths of Study

The strengths of our study include: enhanced statistical power and precision, and the ability to explore and clarify why studies show disparate results. Since childhood leukemia is a relatively rare disease, sample sizes of

some previous studies have been small and the risk estimates have lacked precision. By combining information over different studies, our meta-analysis has more statistical power to detect an effect than an analysis based on one study, resulting in a more precise estimate of effect (i.e., an estimate with a narrower confidence interval), and therefore providing stronger evidence than that derived from any individual study (Figure 8).

Confidence in our overall conclusion (that high birth weight increases the odds of ALL) is also enhanced by the robustness of our findings to different assumptions in the sensitivity analysis. As shown in Figure 12, the exclusion of any individual study had little effect on the overall odds ratio. Furthermore, the overall effect was calculated by different statistical methods, both using a fixed and a random effects model. In the main meta-analysis for ALL, the fixed effects model rendered an odds ratio of 1.24 (95% CI: 1.12, 1.37) while the random effects model rendered an odds ratio of 1.25 (95% CI: 1.11, 1.42). Given the lack of statistical heterogeneity, it is not surprisingly that these estimates are virtually identical with confidence intervals only slightly wider when using the random effects model. This is explained by the relatively small amount of between study variation present in our meta-analysis. Methodological quality was assessed in terms of peer-review status, response rate among cases and controls, and source of birth weight data. Exclusion of non-peer-reviewed studies and studies with < 70% response rate among cases and controls did not change the overall estimate. While exclusion of studies that used maternal interview (rather than birth certificate data) as the source of birth weight information changed the

magnitude of the overall odds ratio the most of all the variables we examined, this change was only marginal (Table 7). Finally, studies varied in choice of threshold for high birth weight (Table 9) but this again had little effect on the overall odds ratio. For example, both the main meta-analysis and the secondary analysis (which differed from the main meta-analysis in including studies with high birth weight cutoffs other than > 4,000 g) show similar results with an overall odds ratio of 1.24 (95% CI: 1.12, 1.37) and 1.29 (95% CI: 1.18, 1.41), respectively. The sensitivity analysis thus shows that the results from our meta-analysis are robust to the influence of any individual study, to the exclusion of studies of lesser quality, and to the choice of high birth weight cutoff. When overall conclusions based on results are robust -- that is, they do not vary but are stable when different assumptions are made -- confidence in the conclusions is increased.

In short, our meta-analysis aggregates the results of several studies that examined high birth weight as a risk factor for ALL. It increases statistical power and precision. It gives an overall perspective on this association while clarifying the reasons why the results of some studies disagree.

4.5. Potential Limitations

Potential bias in our meta-analysis needs to be considered. Publication bias -- the possibility that studies that show non-significant results (e.g., $p>0.05$) or null results (e.g., Odds Ratio=1.0) are not published – is a problem for meta-analyses.[37] Existence of a bias in favor of publication of statistically significant results is well documented. [37] For example, among 285 analyzed studies

reviewed by the Central Oxford Research Ethics Committee in 1984-1987, 154 had statistically significant results and 131 did not.[40] Of the 154 studies with statistically significant results, 60.4% had been published, whereas only 34.4% of the studies that did not have statistically significant results had been published. [40] The problem of publication bias will be solved completely only when all well-conducted studies are accepted for publication irrespective of the statistical significance of their results. Attempts to retrieve unpublished observational studies are difficult. Identification of unpublished studies is most feasible when studies are registered in their planning stages or when they begin. However, unlike experimental studies in which registries of clinical trials exist, registers of observational studies have not yet been created. Without an effective way to identify unpublished observational studies, researchers are left with assessing the presence of publication bias. Publication bias due to the exclusion of studies with null results, if it were present in our meta-analysis, would have resulted in an overestimate of the true effect size. However, we did not find evidence of publication bias based on a variety of graphical and statistical tests (Figure 14 and 15). Therefore, publication bias is unlikely to have distorted our findings.

Besides publication bias, bias within the individual studies upon which our meta-analysis is based also might have influenced our results. Selection bias stems from an absence of comparability between cases and controls. Since non-respondents may be different from respondents, selection bias could have been a problem in studies with low participation among cases and controls. However, in our meta-analysis, studies that reported $\geq$ 70% response rate among cases

and controls demonstrated an overall odds ratio of 1.23 (95% CI: 1.09, 1.39; N=five studies) – a result similar to that of studies that reported < 70% response rate (OR= 1.27; 95% CI: 1.05, 1.53; N=four studies). In case-control studies, controls should represent the population from which the cases are drawn, otherwise selection bias could also distort study results. The studies upon which our meta-analysis are based appears to have used appropriate control groups. Five (56%) studies in our meta-analysis were hospital-based with the cases taken from all patients fulfilling the eligibility criteria and attending a certain hospital or group of hospitals. In these studies, controls were selected from the community (i.e., the catchment area of the hospital) or from the entire population. The remaining four (44%) studies in our meta-analysis used population-based cancer registries to recruit cases. Of these four studies, three utilized population controls while one used community ones.

The tendency of parents of cases to remember exposures to putative risk factors differently than parents of controls leads to recall bias, a form of information bias. Parents of cases tend to search their memories to identify what might have caused disease whereas parents of healthy controls lack such motivation. Such differential recall of past exposures may introduce bias. However, recall bias likely is not a major problem in the present meta-analysis. First, four of the nine studies included in the main meta-analysis used birth certificate records for its birth weight data which eliminates the problem of recall bias because the data were not self-reported after a diagnosis of leukemia. Second, studies have demonstrated that mothers can reliably recall birth weight.

[138,139] Obstetric records (i.e., delivery logs) can be more accurate at recording birth weight than birth certificate data which, in turn, are more accurate than maternal recall. Even so, studies have documented high agreement between maternal recall and obstetric records for infant birth weight. One study that validated maternal recall with medical records (including hospital delivery records) showed that there was 90% agreement.[138] Furthermore, in that same study, both case mothers and control mothers were equally accurate at recalling their child's birth weight. Another study reported a high degree of consistency between maternal recall and medical records or birth certificates.[139] Another study of over 46,000 women, compared maternal recall with birth certificates and found that 89 percent of birth weights were reported within 1 ounce of birth certificate birth weights.[140] In our meta-analysis, studies that used a birth registry as the source of birth weight data showed an overall odds ratio of 1.17 (95% CI: 0.99, 1.38; N=four studies) compared to studies based on maternal interviews (OR=1.35; 95% CI: 1.16, 1.59; N=five studies). Rounding errors and errors from converting pounds to grams could contribute to the differences in these estimates of effect. In our meta-analysis, only three of nine studies described how birth weight data was specifically collected. In two of these studies, birth weight information was provided by maternal recall and reportedly collected in pounds and ounces, and converted to grams.[116,117] In the third study, birth weight was ascertained using birth certificates.[14] In this study, birth weight was recorded categorically in 500 g intervals for part of the study duration while the actual birth weight was recorded for the other part of the study duration. Although birth

weight data may be subject to measurement error, this is likely to be non-differential and therefore, such error, if it occurred, would lead to an attenuation of the true effect of birth weight on ALL risk.

Confounding factors -- factors that are related to both the exposure and the outcome (but not directly involved in the causal pathway) – could also lead to inaccurate results. In a meta-analysis, the investigator has virtually no control over how data from individual studies are collected and recorded. Consequently, important confounders may not have been measured or reported. Failure to adequately control for confounding threatens the validity of study results. Among the nine studies included in our meta-analysis, two (22%) adjusted for or matched on age (i.e., birth date), gender, and race; three (33%) adjusted for or matched on age and gender; and four (44%) adjusted for or matched on just a single variable (i.e., either age, gender, or race alone). In total then, seven of nine studies did not adequately control for confounding. Not controlling for gender would enhance the birth weight effect, since males are heavier at birth and there are more males than females with ALL. Not controlling for race would also enhance the birth weight effect, since white populations are heavier at birth and more whites develop ALL than other ethnic groups, particularly blacks. Even if adjustments for important potential confounders were made in all of the original studies, residual confounding could remain a potentially serious problem. Residual confounding arises whenever a confounding factor cannot be measured with sufficient precision or sufficiently adjusted for in the analysis.

On one hand, results of a meta-analysis are no more reliable than the quality of the underlying studies upon which they are based. While combining data decreases the variation caused by random error (by increasing the sample size), it does not eliminate or reduce any systematic error (i.e., bias).[37] In other words, meta-analysis cannot compensate for bias or confounding in the original studies. In our meta-analysis, we found evidence of inadequate adjustment for confounding among seven of nine studies. Thus, even when a statistically significant association is observed, it is still possible that the association is due to chance, bias, or confounding. With large odds ratios (such as an approximately 20-fold increase in acute leukemia among children with Down syndrome) it is much less likely that chance, undetected bias, or confounding could explain the entire increase. With relatively small odds ratios (such as 1.24 in our meta-analysis), it can be difficult to distinguish a true association from one that is attributable to chance, undetected bias, or confounding.

On the other hand, the consistency of findings across studies included in our meta-analysis and the replication of our results by a completely separate meta-analysis, enhances confidence in the association between ALL and high birth weight. Furthermore, this association seems to be consistent across times and geography. Studies have now been conducted in a variety of locations within the United States, as well as outside – in the United Kingdom, Sweden, France, Germany, Greece, Denmark, North Ireland, Scotland, and China. In addition to consistency of findings, the association between birth weight and ALL appears to follow a log-linear dose-response relationship. In their meta-analysis, Hjalgrim

and colleagues found a statistically significant log-linear relation between birth weight and risk of ALL (odds ratio=1.14/1,000 g increase in birth weight; 95% CI: 1.08,1.20). [94]

4.6. Methodological Issues of Meta-analysis as a Technique

In this section, several methodological issues concerning meta-analysis as a technique are highlighted. A comparison between our meta-analysis and another one conducted by Hjalgrim and colleagues is also described.

4.6.1. Importance of broad literature search using multiple database sources

A comprehensive literature search is an essential ingredient of high-quality meta-analysis. The inclusion of all relevant studies is crucial to avoid bias and maximize precision. The availability of Medline and other computer-stored bibliographic databases has greatly facilitated the identification of relevant published studies. Medline contains information on publications in approximately 3,900 biomedical journals in 40 languages and covers the period from 1966 to the present. [37] While Medline is the primary source of information on publications in the biomedical literature, it provides only part of the total information. No single computerized database covers all periodicals. For example, our meta-analysis underscores the importance of a broad and comprehensive literature search using a number of sources. The use of four other databases besides Medline enabled discovery of over 300 unique citations not indexed in Medline. Furthermore, a total of four eligible studies would completely have been missed

without a search of other databases beyond Medline and a review of references listed in eligible studies. Medline contains information on original research reported in less than one third of all biomedical journals. Journals that are not indexed in Medline are described as those that are highly specialized, on topics considered to be of limited interest; journals of low circulation, and journals in which articles have not been peer-reviewed.

4.6.2. Need for explicit definitions and criteria

A critical characteristic of meta-analysis is development of systematic, explicit procedures for identifying studies with relevant data. In being systematic, the procedures reduce bias. In being explicit, the procedures help to ensure reproducibility. The goals of defining eligibility criteria are to ensure reproducibility of the meta-analysis and to minimize bias in selection of studies for the meta-analysis. Another investigator faced with the same body of literature applying the same eligibility criteria should choose the same set of studies. For instance, the criteria for choosing among results of multiple publications from the same study population should be explicitly defined otherwise reproducibility could be jeopardized. A case in point involves two sets of original studies that were duplicates of each other. Hjalgrim's meta-analysis which did not describe the criteria for choosing between duplicate studies, choose one set of studies while our meta-analysis choose a different set of studies based on *a priori* criteria.

Explicit and detailed methods are also necessary to discern duplication of data. It is not always obvious that multiple publications come from a single study, and one set of study participants may thus be included in a meta-analysis twice.

For example, our meta-analysis originally included a study[23] that was later identified as a duplicate by an expert familiar with the study. The methods section of this particular study did not report in sufficient detail information to permit identification of its duplicate status. Without expert guidance, a meta-analyst would not have known that this study was a duplicate based solely on what was reported in the study. In a meta-analysis, only one estimate of effect from each eligible study should be used in the calculation of the summary estimate of effect because using more than one would inappropriately weight studies with many estimates of effect. Therefore, it is essential that original studies provide information in as much detail to permit identification of duplication.

4.6.3. Statistical heterogeneity versus clinical heterogeneity

Exploration of heterogeneity should go beyond the performance of statistical tests to include an examination of clinical heterogeneity. Clinical heterogeneity refers to differences in the characteristics of the study designs, and study subjects (such as their mean age) as well as to differences in the effect of the exposure in different subgroups of patients. [37] Statistical heterogeneity may arise because of clinical heterogeneity but it could also be due to chance. The exploration of clinical heterogeneity has two distinct components -- one methodologic and the second biologic -- to assess the possibility of biologic effect modification. In a meta-analysis, lack of statistical heterogeneity does not necessarily make it appropriate to combine results; clinical heterogeneity should be considered as well. For example, in our meta-analysis, the outcomes

considered were ALL, AML, and leukemia unspecified (for studies that did not differentiate among leukemia type). While combining studies that examined ALL with studies that examined leukemia unspecified failed to find statistical heterogeneity, there may be sufficient clinical heterogeneity to warrant that study results are not combined across the different outcomes.

4.6.4. Need for careful attention to reference group of exposure variable

In conducting a meta-analysis, careful attention to the choice of exposure and outcome variables and how they are defined is critical. Equally important but not as well underscored, is the significance of the reference group for the exposure variable. For example, in our meta-analysis choice of reference birth weight changed the strength of the association between birth weight and ALL (Table 9). Compared to an overall odds ratio of 1.24 (95% CI: 1.12, 1.37) when the reference was all newborns weighing less than 4000 g, the odds ratio changed to 1.13 (95% CI: 0.96, 1.32) when newborns weighing from 2500-4000 g were the referent category. The odds ratio changed to 1.21 (95% CI: 0.96, 1.52) when only newborns weighing 3000-3500 g were considered; to 1.40 (95% CI: 1.10, 1.80) when only < 3000 g was the referent category; and finally the odds ratio changed to 1.37 (95% CI: 1.10, 1.69) when only < 4000 g was the referent category (Table 8).

4.6.5. Comparison of Hjalgrim meta-analysis vs. Taylor meta-analysis

After the written completion of the methods of this present meta-analysis by Taylor, a meta-analysis by Hjalgrim and colleagues was published that also examined observational studies of birth weight as a risk factor for childhood leukemia. Table 10 highlights how the two studies compare.

In the literature search Hjalgrim used Medline and Embase, while we used these two databases along with Cancerlit, Current Contents, and Dissertation Abstracts Online. Search terms in Hjalgrim's study were more numerous and had a more restrictive effect than the terms used in ours. Inclusion criteria by Hjalgrim did not specify study design nor the kind of study population as ours did.

At the same time, both meta-analyses defined high birth weight as $\geq$ 4000 g. Our choice of definition was based on the medical definition of macrosomia. The term macrosomia implies fetal growth beyond a specific weight regardless of gestational age.[142] The most widely used definition is $\geq$ 4000 g even though definitions have varied from $\geq$ 4000 g to $\geq$ 4500 g and[142-144] despite the fact that in 1991, the American College of Obstetricians and Gynecologists suggested that macrosomia be defined by birth weight of 4500 g or more.[145] Several medical complications are associated with birth weight $\geq$ 4000 g. Although rare (complicating 1.4 percent of all vaginal deliveries), shoulder dystocia is the most serious complication associated with macrosomia. Approximately one-half of all cases of shoulder dystocia occur in babies weighing $\geq$ 4000 g.[146] In addition, when birth weight is more than 4000 g, the risk of brachial plexus injury to the neonate is increased by 9.6 times in pregnant women with diabetes.[147] Furthermore, increased risk of cesarean delivery is the primary maternal risk factor associated with macrosomia. A second reason we choose 4000 g as the cutoff for high birth weight in our meta-analysis is that in the scientific literature on ALL and birth weight, 4000 g is the most frequently used threshold for high birth weight.

While the definition for high birth weight was the same in both meta-analyses, the reference birth weight differed. Hjialgrim used a birth weight cutoff of 4000 g and extracted data from each study on the number of cases and controls with birth weights above and below this value. Corresponding crude odds ratios were then calculated. For example, Table 11 depicts the original analysis by Shu and colleagues while Table 12 shows the re-analysis of this data by Hjalgrim.[22] While this allowed Hjalgrim to obtain a uniform measure of association across studies with a standardized dichotomous comparison ($\geq$ 4000 g vs. < 4000 g), it also resulted in effectively ignoring the matching status of the original study design. The majority of the included studies were individually matched case-control studies. We did not follow this method. Instead, we kept the choice of reference birth weight and used what was reported by the authors. Matching imposes comparability for a certain factor thus ensuring the same prevalence of that factor in the cases and controls. Matching on a certain factor eliminates its influence as a possible confounder. A matched study design requires a different type of analysis from unmatched studies in which the odds ratio calculation considers only the discordant pairs. Failure to match in the analysis of a matched study results in attenuation of the odds ratio.

The outcome variable for ALL was also defined differently by the two meta-analyses. With the rationale that because about 80% of leukemia cases arising in childhood are ALL, study-specific odds ratios for ALL and leukemia unspecified were combined and considered together by Hjalgrim. Because AML and ALL are biologically heterogeneous with some different risk factors, we chose to analyze

ALL studies separately from those that examined AML or leukemia unspecified. One of the most critical decisions about eligibility for a meta-analysis is the decision about how similar the exposures and the outcome must be to use them in the same analysis. When exposure has an effect on one outcome but not on another, including all of the studies may also bias the summary estimate of effect.

Based on their respective inclusion criteria, Hjalgrim identified 13 studies (7 studies of ALL plus 6 studies of leukemia unspecified) to include in a meta-analysis while we identified 9 studies of ALL. Four studies were included by both our meta-analysis and Hjaligrim's.[22,24,33,115] Three of these four studies[22,24,33] ranked the top three largest studies in both meta-analyses.

Nine studies were included in Hjalgrim but not in ours because:

- Six had outcomes too broad (were leukemia unspecified),
- One was a duplicate,
- One had a different cutoff for high birth weight (> 4,010 g rather than 4,000 g), and
- One was a case-referent study which compared birth weights in cases with external birth weight distribution data rather than a control group.

The criteria for choosing among studies that are duplications was not described by Hjalgrim. We defined the criteria as the most recent or most complete study.

Finally, while many features are different, Hjalgrim's meta-analysis and the one we conducted found virtually similar results, with overall odds ratios of 1.26 (95% CI: 1.17, 1.37) and 1.24 (95% CI: 1.12, 1.37), respectively.

Table 10. Comparison of Meta-analyses by Hjalgrim vs. Taylor by Selected Features

Feature	Meta-analysis by Hjalgrim	Meta-analysis by Taylor
Databases used in literature search	Medline and Embase	Medline, Cancerlit, Current Contents, Embase, Dissertation Abstracts Online
Search terms	- child - leukemia - cancer - epidemiology - risk factor - case control - cohort - birth weight	- child - acute leukemia - risk factors - birth weight
Inclusion criteria	- number of individuals (both cases & controls) in different birth weight strata, and - measures of relative risk for leukemia (unadjusted or adjusted odds ratios)	- a case-control or cohort study - pediatric study population (< 15 yrs) - studies that reported relative risk or relative odds of leukemia, ALL or AML associated with high birth weight ($\geq$ 4000 g) or that provide data in which relative risk or relative odds could be calculated
Threshold for high birth weight cutoff	$\geq$ 4000 g	$\geq$ 4000 g
Referent birth weight	< 4000 g Redefined referent group and calculated new crude odds ratio	< 4000 g or < 3000 g or 3000-3499 g or 2500-4000 g Used referent group as defined by authors
Outcome for ALL	ALL + unspecified leukemia incidence and mortality	ALL incidence
Total studies included in ALL meta-analysis	13 (7 studies of ALL + 6 studies of unspecified leukemia)	9 studies of ALL
Criteria for choosing among studies that are duplications	Not defined	Most recent or most complete study selected
Overall odds ratio for ALL and high birth weight	1.26 (95% CI: 1.17, 1.37; N=13 studies of ALL + unspecified leukemia)	1.24 (95% CI: 1.12, 1.37; N=9 studies of ALL)

Table 11. Odds ratios of childhood ALL associated with birth weight as reported by Shu[22]

Birth weight	Cases	Controls	Odds Ratio (95% CI)
$\leq$ 3000 g	326	376	1.0 (ref.)
3001-3500 g	628	685	1.9 (0.9-1.3)
3501-4000 g	607	680	1.1 (0.9-1.4)
> 4000 g	278	244	1.4 (1.1-1.8)

Table 12. Re-analysis of data in Table 11 by Hjalgrim

Birth weight	Cases	Controls	Odds Ratio (95% CI)
≤ 4000 g	1561	1741	1.0 (ref.)
> 4000 g	278	244	1.27 1.06-1.53)

4.7. Public Health Significance

Acute leukemia is the most predominant form of cancer in children, with poorly understood causes and risk factors. Results of previous investigations examining high birth weight as a risk factor for childhood ALL have been inconsistent. The present meta-analysis is significant in that it: (1) elucidates the mixed evidence in the literature while advancing scientific understanding, (2) guides clinical practice and policy, (3) identifies gaps in the technique of meta-analysis and emphasizes certain reforms in the methodology of this study design and (4) provides a comparison for a pooled analysis on the same topic currently underway.

First, our meta-analysis clarifies the mixed evidence in the scientific literature concerning the relationship between high birth weight and ALL by providing a more precise estimate of effect and explaining inconsistencies among studies. Since childhood malignancies are relatively rare diseases, sample sizes of previous studies were often small and the resulting risk estimates lacked precision. By combining information over different studies, our integrated analysis of nine case-control studies found that high birth weight increased the odds of childhood ALL by 24%. As the second of two meta-analyses, our study confirms the results of the other meta-analysis, thereby strengthening the evidence of a high birth weight-ALL association.

Second, findings from our meta-analysis could influence clinical practice and public health policy. While the results of our study add to the accumulating evidence that establishes high birth weight as a risk factor for childhood ALL, the biologic foundation of this association remains unclear and the preventive implications of these findings thus remain elusive. If the association between high birth weight and childhood ALL is causal, then clinicians may consider changes in their recommendations given to female patients regarding those factors which could influence high birth weight in their babies. Alternatively, if high birth weight is simply a marker for some other exposure, then modifying birth weight might not change the risk of acute leukemia in children.

Many of the determinants of high birth weight cannot be changed or treated. Some however, such as weight gain during pregnancy, is potentially amenable to change. Greater weight gain during pregnancy is associated with higher birth weights. One study reported that women who gained 24-33 pounds and over 33 pounds during pregnancy had 1.77 times and 2.86 times the risk, respectively, of having a heavy baby (> 4,000 g) than women who gained less than 14.9 pounds.[54] Therefore, if the association between high birth weight and ALL is causal, then interventions that lead to optimal weight gain may play an important role in reducing the prevalence of high birth weight babies and thus, reduce the risk of acute leukemia. The importance of periodic monitoring of prenatal weight gain in women is underscored.

In 1990, the Institute of Medicine (IOM) published a recommendation to base total weight gain and pattern of gain on pre-pregnancy body mass index

(BMI), as shown in Table 3.[55] Current IOM recommendations for optimal weight gain may place women who follow these recommendations at higher risk for having high birth weight babies. Confirming the link between high birth weight and acute leukemia to be causal would warrant careful review of weight gain recommendations for pregnancy.

While the increase in odds of childhood ALL associated with high birth weight may be relatively small (24%), it may potentially be of great public health importance because of the large numbers of babies with high birth weight with a resulting potential for acute leukemia. According to the National Center for Health Statistics (NCHS), about 9.4% of children born in the United States in 2001 had high birth weight (> 4,000 g).[57] If high birth weight is indeed a risk factor for childhood acute leukemia what would be the impact of reducing birth weight on the incidence of ALL? In other words, what is the etiologic fraction or the population attributable risk of high birth weight on ALL? Given our study's finding of an odds ratio of 1.24 and using 9.4% as the proportion (p) of children with high birth weight, the population attributable risk (PAR) is 2.2% (PAR = [p (r-1)] / [p (r-1)+1]). In other words, approximately 2.2% of ALL in children may be attributable to high birth weight, and presumably could be prevented by decreasing birth weight. High birth weight is associated with other malignancies such as Wilms' tumor, astrocytoma, neuroblastoma, and breast cancer as previously noted. Therefore, the impact of decreasing birth weight may go beyond ALL.

Third, our present meta-analysis identifies gaps in the technique of meta-analysis and emphasizes certain reforms in the methodology of this study design.

As discussed in the previous section 4.7 our meta-analysis underscores the importance of a broad literature search using multiple database sources, the need for explicit definitions and criteria, the consideration of clinical heterogeneity even when statistical heterogeneity warrants combining study results, and the need for careful attention to the reference group for exposure variables.

Fourth, our meta-analysis provides a comparison for a pooled analysis currently underway by Dr. Forman and colleagues. A pooled analysis of individual patient level data from different studies has some advantages over a meta-analysis including the ability to adjust for the same confounders using the same statistical model. However, it is more expensive, time-consuming, and requires the willingness of investigators to provide data for inclusion in the pooled study. Few studies have examined how pooled analysis and meta-analysis on the same topic compare.

4.8. Recommendations and Conclusion

Based on a meta-analysis of nine case-control studies on high birth weight as a risk factor for childhood ALL, the following recommendations are made:

1. Women who are pregnant or considering pregnancy should know that unbounded weight gain may increase the odds of childhood ALL in their baby.
2. Authors of original studies should explicitly report definitions, criteria, and other information to permit identification of duplicate studies.
3. Researchers conducting meta-analysis should use multiple database sources to search for relevant literature, consider clinical heterogeneity

along with statistical heterogeneity, and pay careful attention to the reference groups for exposure variables.

4. Editors should publish all well-conducted studies regardless of results or their statistical significance.
5. Registries for both published and unpublished, funded and un-funded observational studies should be created to facilitate pooling, meta-analysis, and collaborations between investigators.
6. More research is needed to investigate the mechanism of action of high birth weight on ALL (i.e., whether high birth weight is part of the causal pathway or acts as a surrogate marker).

In conclusion, since its identification 150 years ago, substantial advances have been made in the diagnosis and treatment of childhood leukemias, and in employment of newer classification schemes. Advances in laboratory procedures and diagnostics have enabled identification of subtypes within ALL and AML. This heterogeneity of both ALL and AML has been demonstrated through study of the biologic characteristics, especially cytogenic and molecular, of leukemic cells. This information has been effectively applied in ALL to develop risk-adapted therapies to ensure that patients with high-risk disease receive intensive treatment, while those with lower-risk features receive less toxic therapy. Relatively less progress has been achieved in confirming causative factors. Despite studies conducted over more than four decades, the etiology of childhood leukemia remains largely unknown. Established risk factors can explain only a very small proportion of childhood leukemias. The findings

presented here contributes to the accumulating body of evidence that high birth weight increases the odds of childhood ALL. This meta-analysis confirms high birth weight as an established risk factor and is in accord with another meta-analysis on the same topic. Whether high birth weight causes childhood ALL or simply is a marker for it remains unclear. Growth hormones in intrauterine life, such as insulin-like growth factor-1 (IGF-1), could very well play a role in the association between ALL and high birth weight. The positive association of IGF-1 with birth weight is already documented. Hypothetically, increased in utero exposure to IGF-1 could at the same time, increase the total number of stem cells, and, by extension, the total number of replicating immature cells and eventually the number of cells at risk for malignant transformation. Such a link could offer a plausible biological mechanism underlying the early life roots of childhood acute leukemia. Although survival for children with ALL is now extremely high (due to improvements in treatment), incidence of ALL continues to increase with a deficient understanding of etiology. This trend underscores the urgency and import of additional research to illuminate and confirm specific biological mechanisms of childhood acute leukemia.

Appendix A. Initial Screening of Potentially Eligible Studies

ID No.	Birth weight (Y/N)	Leukemia, ALL, or AML (Y/N)	Case-control or cohort (Y/N)	Age range of study group	Cutoff for high birth weight	Birth weight stratified (Y/N)	RR, OR or data to compute (Y/N)	Meets inclusion criteria* (Y/N)	Contact authors? (Y/N)

*** Inclusion Criteria**

- a case-control or cohort design,
- pediatric study population (< 15 yrs)
- relative risk or relative odds of leukemia, ALL or AML associated with high birth weight (> 4000 g) or that provide data in which relative risk or relative odds could be calculated
- individuals (both study and comparison groups) in different birth weight strata

Appendix B. Data Abstraction Form

Reviewer: _____ Date of Review: _____

1. ID number	
2. Authors' name	
3. Publication year	
4. Study type	
5. Country	
6. Leukemia outcome (mortality or incidence)	
7. Leukemia type (ALL, AML, or leukemia)	
8. Diagnosis of leukemia (e.g., pathology, self-report, etc.)	
9. Cutoff for high birth weight	
10. Birth weight source (e.g., interview, registry, etc.)	
11. Number of cases	
12. Source of cases (e.g., cancer registry, hospital records, etc.)	
13. Age range of cases	
14. Case recruitment period	
15. Number of controls	
16. Source of controls (e.g., population, community, hospital, etc.)	

ID number _____

17. Unadjusted OR or RR with 95% CI for 4000 g. cutoff (specify outcome)	
18. Adjusted OR or RR with 95% CI for 4000 g. cutoff (specify outcome)*	
19. Adjusting variables	
20. Stratification by age	
21. Stratification by dose	
22. Matching variables	
23. Duration of follow-up (for cohort studies)	
24. Losses to follow-up	
25. Participation rate of controls	
26. Participation rate of cases	
27. Peer reviewed journal (Y/N)	
28. Additional references	
29. Potential duplication (Y/N)	
30. Miscellaneous	

* If more than one adjusted estimate of effect, choose the "most adjusted" estimate (i.e., one with the largest number of variables in the model)

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